Abstracts
09–12 May 2018

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Upper gastrointestinal involvement is not predictive of disease course in pediatric Inflammatory bowel disease of colitis phenotype

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Objectives and Study: Upper Gastrointestinal (UGI) involvement is an established predictor of disease course in Crohn’s disease (CD) but similar data in ulcerative colitis (UC) are conflicting. Scarce data exist on the predictive value of UGI findings in IBDU. Being an intermediate phenotype between CD and UC it is unknown whether IBDU is more similar to CD or UC in that regard. We therefore aimed to describe the UGI findings of a sizeable cohort of children with IBDU compared to children with UC and CD with emphasis on predicting disease course. We used isolated Crohn’s colitis (CC) phenotype to allow meaningful comparisons between the groups while avoiding confounding effect of disease location.

Method: Data were retrospectively collected from 23 pediatric centers in Europe and Israel affiliated with the Paediatric IBD- Porto group of ESPGHAN via electronic case report forms, including children 2-18 years of age with isolated colonic IBD and available follow-up of at least 1 year. Ileocolonoscopy and, regardless of symptoms, esophago-gastro-duodenoscopy (EGD) were performed in all patients at diagnosis. EGD were explicitly reviewed for macroscopic UGI involvement (i.e. erythema, scalloping, nodularity, aphthous ulcerations and overt ulcerations) at each anatomic segment. The severity of disease course was scored by longitudinal physician global assessment using standardized definitions (PGA; quiescent, very mild, mild, moderate and severe). The need for intensified treatment was defined as the need for biologics, cyclosporine, tacrolimus, and/or surgery.

Results: 798 patients were included: 290 with UC, 252 with CC and 256 with IBDU. Median age was 11.5±3.7 years, median disease duration 2.9 years (IQR 1.6-4.1) and 59% male. A total of 311 (39%) patients had any macroscopic UGI involvement, more prevalent in the CC group (n=127 (50%)), then IBDU (n=101 (40%); p=0.016) and least in the UC group (n=83 (29%); p=0.009 compared with IBDU and p&LT; 0.001 with CC). The gastric region was the most commonly involved site (n=238 (30%)). UGI findings (any or at a specific UGI site) were not associated with intensified treatment for any of the IBD-phenotypes (IBD-U p=0.51, CC p=0.54 and UC p=0.12). Results were similar if using only presence of aphthous or overt ulcerations at any site of the UGI tract. Similarly, there was no significant association between UGI findings and longitudinal PGA score for any of the IBD phenotypes (IBDU p=0.06, CD p=0.73, and UC p=0.47).

Conclusion: In this large cohort of children with colonic IBD, UGI findings were common in all three IBD phenotypes with the rate being intermediate in IBDU. Macroscopic UGI findings were not associated with disease course measured by either need for intensified treatment or by longitudinal PGA. These data suggest that UGI involvement should not be considered as a poor prognostic factor when considering treatment intensity in colitis phenotype. Further studies are required to elucidate whether the previously reported predictive value of UGI findings in CD is driven by small bowel involvement of the disease.

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Deciphering EGF pathway in familial adenomatous polyposis through human organoid culture is promising

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Objectives and Study: To date, no model adequately reproduces human familial adenomatous polyposis (FAP). Mice deficient for Adenomatous polyposis coli (Apc) develop intestinal instead of colonic polyps. Wnt/APC/β-catenin pathway is a main pathway involved in intestinal stem cell (ISC) renewal and proliferation. Since colonic organoids, a 3D epithelial culture, is based on ISC properties, we investigated its relevance as a model to study FAP. We evaluated the impact of epidermal growth factor (EGF), which is another important growth factor present in the organoid culture medium.

Method: During colonoscopy, we performed biopsies in FAP patients (n=7), from adenomatous (A) and non-adenomatous (NA) areas, and in healthy controls (HC, n=6). These biopsies were cultured in specific conditions to develop organoids. As we previously reported, FAP organoids were cultured without Wnt3a. At D2, we performed an EGF deprivation. Organoid development was monitored during one week. At that time, we performed immunofluorescence, western blots and qPCR analyses. This study had the agreement of the Ethics Committee.

Results: We found well-described organoids (immature cysts, colonospheres, and colonoids), and a new one characterized by budding structures in cysts, which is only present in A culture. Immunostaining of CD24/CD44 (immaturity) and Ki67 (proliferation) were increased in FAP compared to HC organoids.

We determined an important role of EGF. Its deprivation blocked all organoid growth, but it only increased the mortality of A organoids. A proteomic screening suggested an activation of MAPK pathway in NA and HC under control of EGF, while it was not activated neither altered by EGF deprivation in A organoids. Using inhibitors of Wnt ligands (IWP12) and TGFb (LY2157299), with or without EGF, we found that another Wnt ligand and TGFß were involved in A organoids growth. The effect of TGFß and EGF was mediated by Ser552-bcatenin phosphorylation, which is independent of APC. Finally, a main finding of genomic analysis was a 50% decrease of Epiregulin in A organoids after EGF deprivation.

Conclusion: Organoid culture is relevant to study FAP. It revealed that ISC of adenomatous area were dependent of EGF and it should allow discovering new potential therapeutic targets (TGFß via PI3K (p110alpha), Epiregulin).

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GASTROENTEROLOGY - Enteropathy (other than Coeliac disease)

G-O-003

Aberrant lipid metabolism in patients with DGAT1 deficiency

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Objectives and Study: Congenital diarrhoeal disorders (CDD) are rare disorders of the gastrointestinal system that can be attributed to numerous monogenic aetiologies. Recently, mutations in DGAT1 have been identified in patients with a form of CDD that involved early-onset protein-losing enteropathy (EO-PLE), but the underlying molecular pathomechanism of DGAT1 deficiency has remained largely elusive.

Method: We studied 9 patients from 6 unrelated pedigrees suffering from intestinal failure, including early-onset severe diarrhoea, hypoalbuminemia, and sometimes fatal PLE that segregates perfectly with the disease in an autosomal recessive fashion. We performed whole exome sequencing to identify genetic disease aetiologies. We analysed DGAT1 variants in patient-derived fibroblasts and intestinal organoids. We confirmed the phenotype through rescue by exogenous expression of DGAT1 in patients’ fibroblasts and CRISPR/Cas9-guided deletion of DGAT1 in healthy control intestinal organoids.

Results: We identified 5 novel bi-allelic loss-of-function mutations in the gene DGAT1 encoding diacylglycerol-acyltransferase 1. DGAT1 catalyses the formation of triglyceride from diacylglycerol and acyl-CoA. The mutations led to severely reduced or absent protein expression, resulting in lack of lipid droplet formation after treatment with oleic acid in patient derived fibroblasts and intestinal organoids. Using lipid chromatography, we show that DGAT1 deficiency specifically altered triglyceride metabolism. Exogenous DGAT1 reconstitution, and intriguingly exogenous DGAT2 expression rescued lipid droplet formation in fibroblasts.

Conclusion: We here identified the largest cohort of DGAT1-deficient patients thus far, linking DGAT1 deficiency to altered lipid metabolism and fat intolerance. For the first time, we show the importance of DGAT1 in gut epithelium, and that exogenous DGAT1 and DGAT2 expression could rescue aberrant lipid metabolism in patient cells. We highlight the importance of identifying known CDD-causing monogenic defects in sequencing of patients with intestinal failure for correct genetic diagnosis.

vR, A, K, H., and vH-V are shared first authors, and J, M, and B are shared senior authors.
GASTROENTEROLOGY - Cystic fibrosis and pancreatic disorders

G-O-004

Functional and morphological recovery is incomplete after acute and acute recurrent pancreatitis in children

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Objectives and Study: Outcome after an acute attack of pancreatitis is well documented in adults, but there is a lack of data in children after acute (AP) and acute recurrent pancreatitis (ARP). We prospectively evaluated the morphology and functional impairment of pancreas after recovery from pancreatitis.

Method: In this prospective cohort study, all consecutive patients presenting with acute (n=61) or acute recurrent pancreatitis (n=35) as per standard case definition were enrolled between March 2015 and October 2016. After 4 months of pancreatitis, fecal elastase-1(µg/g) and 2-hour oral glucose tolerance test (OGTT) to calculate oral disposition index (DIo) (calculated as [insulinogenic index (IGI30)/I0]mmol/L; where, IGI30=ΔI30-I0/ΔG30-G0; G=Glucose(mmol/L) and I=insulin(pmol/L) at 0 and 30 minutes) for beta cell function (endocrine) were done. Morphology changes were assessed by endoscopic (EUS) and transabdominal ultrasound (TUS). Patients with chronic pancreatitis (CP) (n=27) and healthy children (HC) (n=26) were included as controls for FE-1 and OGTT.

Results: At a median follow up of 12 (4-44) and 11 (2-108) months, 66.7% and 75.9% (p= 0.57) of AP and ARP demonstrated exocrine insufficiency (FE-1< 200) respectively. Mean (SD) FE- 1(µg/g) were 183.64±150.94(AP), 135.70±103.80(ARP), 46.56±30.20(CP), 240.00±181.83(HC) (p< 0.001; ANOVA) [AP vs CP, ARP vs. CP, CP vs. HC, (p< 0.001)]. Impaired glucose tolerance was seen in 16.6% and 22.6% (p= 0.56) of AP and ARP, which was due to insulin resistance. Median (IQR) DIo (mmol/L⁻¹) was comparable between AP [4.20(2.36,8.3)] and HC [5.20(2.89,8.68)], but was low in ARP [2.97(1.80,5.12)] which was comparable to CP [1.91(1.20,2.83); p=0.06] and significantly lower than HC [(2.97(1.80,5.12) vs. 5.20(2.89,8.68)); p=0.02]. There was no correlation between FE-1 and DIo (r=0.18, p=0.19). Morphological changes were noted in 25% and 37% (p=0.34) of AP and ARP respectively. Considering age, gender, severity, fluid collection, presence of risk factors, EUS and TUS abnormality, pseudocyst only the presence of fluid collection (APFC and ANC) predicted exocrine insufficiency [OR, 95% CI; 8.69(2.21-42.94)], whereas no predictor was identified for low DIo.

Conclusion: There was high frequency of biochemical evidence of exocrine insufficiency, with APFC and ANC as a risk factor. Beta cell function is preserved among AP, but poor among ARP (low DIo). One third of the patients demonstrated morphological abnormalities. Pancreatic functional impairment starts before clinical manifestation with exocrine functions affected earlier than endocrine. DIo needs further validation as marker of beta cell function in children with pancreatitis and can be used for assessing risk of future diabetes in cohort of pancreatitis.
### Table 1: Exocrine and endocrine functions

<table>
<thead>
<tr>
<th></th>
<th>AP (n=60)</th>
<th>ARP (n=35)</th>
<th>CP (n=27)</th>
<th>Control (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Range); months follow up</td>
<td>12 (4-44)</td>
<td>11 (2-108)</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Exocrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal Elastase; μg/g (mean±SD)(n)</td>
<td>183.64±150.94 (33)</td>
<td>135.70±103.80 (29)</td>
<td>46.56±30.20 (16)</td>
<td>240.00±181.83 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired</td>
<td>7 of 42 (16.6%)</td>
<td>7 of 31 (22.6%)</td>
<td>10 of 27 (37%)</td>
<td>4 of 26 (15.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>6 of 27 (22.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Oral disposition index (DiO); mmol/L·1; Median (IQR)</td>
<td>4.20(2.36,8.3)</td>
<td>2.97(1.80,5.12)</td>
<td>1.91(1.20,2.83)</td>
<td>5.20(2.89,8.68)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- APFC: Acute peripancreatic fluid collection
- ANC: Acute necrotic collection

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Gluten intake and risk of celiac disease: Preliminary data from an at-risk birth cohort

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Objectives and Study: Few studies have examined gluten intake after infancy as a risk factor for celiac disease (CD). We aimed to determine the association between gluten intake through childhood and CD development.

Method: Since 1993, the Diabetes Autoimmunity Study in the Young (DAISY) cohort in Denver has prospectively assessed the diets of 1,758 children genetically at risk for CD. By January 2017, 152 participants had been identified with CD-autoimmunity (CDA, persistent tTGA positivity) via tissue transglutaminase (tTGA) screening; of these, 83 fulfilled CD-criteria of biopsy-verified histopathology or persistently high tTGA levels. Using validated food frequency questionnaires we determined gluten intake (grams/day) yearly from age 2 years through childhood. Survival analyses with updated, time-dependent exposure were used to estimate hazard ratios adjusted for potential confounders (aHR).

Results: At baseline, the average daily gluten intake was 6.6 (SD, 1.7) grams among participants in the lowest third and 18.2 (4.2) grams in the upper third with an overall average of 11.2 (5.5) grams. Children in the highest third of recent gluten intake had a 2-fold greater hazard rate of CDA (aHR 2.13; 95% confidence interval [CI], 1.18-3.83), than those in the lowest third. The aHR for CDA per gram increase in daily intake was 1.07 (95% CI, 1.02-1.12); this corresponds to an aHR of 1.29 (95% CI, 1.07-1.55) for the four grams of gluten provided in a slice of bread. Similar association patterns as above were found with the development of CD (Figure 1). Looking specifically at the first five years of life, the aHRs for CDA respectively CD were broadly consistent with the results for the complete follow-up period (Figure 1).
Conclusion: Preliminary data from this observational study suggest that the most recently-reported gluten intake level predicts onset of CDA and CD in children at risk for the disease.
Non-invasive biomarkers for assessment of villous abnormalities in patients with coeliac disease and other enteropathies: An alternative to mucosal biopsies

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Objectives and Study: While villous atrophy is hallmark of coeliac disease (CeD), demonstration of which however requires endoscopy. There is a need of non-invasive biomarker both for diagnosis and monitoring of villous atrophy.

Method: Levels of citrulline (synthetic marker of enterocytes) and I-FABP (marker for enterocytic injury) in plasma and regenerating gene-1α (Reg1α) (marker of enterocyte regeneration) in serum were estimated in treatment-naïve patients with CeD (n=131), other enteropathies (n=46), healthy controls (n=216) and disease controls (n=133). Expression of I-FABP and Reg1α were also done in duodenal biopsies using immunohistochemistry and quantitative PCR. In order to validate citrulline synthesis in intestinal mucosa, expression of pyrolline-5-carboxylate synthase (P5CS), a rate limiting enzyme in citrulline synthesis, was performed. To further confirm validity of above markers, a human model was selected having cycles of enterocyte injury and recovery such as patients with haematological malignancies receiving high-dose chemotherapy for HSCTs (n=70) and their samples were obtained at various time points both before and after HSCT.

Results: Citrulline levels in plasma and expression of P5CS in tissue were significantly lower in CeD as compared to controls (p< 0.001), levels increased significantly after GFD. While plasma I-FABP and serum Reg1α levels was significantly higher, tissue expression of both was lower in CeD as compared to controls. Plasma I-FABP and serum Reg1α levels decreased and their respective tissue expression increased after GFD. In human model of enteropathy, citrulline levels followed a cyclical pattern of enterocyte injury and recovery, which corresponded to total leucocytes count in circulation. Optimal cut off of citrulline was ≤30µM/l (sensitivity 78% and specificity 95%) and I-FABP was ≥1100pg/ml (sensitivity 40% and specificity 95) to discriminate between normal and atrophied mucosa.

Conclusion: Consistent changes in citrulline levels in all above experimental groups suggests that citrulline level estimation is the most reliable marker for predicting presence of villous abnormalities and its potential for avoiding biopsies in approximately 78% of subjects with specificity of 95%.

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GASTROENTEROLOGY - Coeliac disease

G-O-007

ESPGHAN non-biopsy criteria have 100% accuracy for celiac disease: a prospective multicenter study applying standardized duodenal morphometry

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Objectives and Study: The 2012 ESPGHAN guidelines for celiac disease enable non-invasive diagnosis in symptomatic children having transglutaminase 2 antibodies (TG2ab) ≥10 times upper limit of normal (ULN) with positive endomysium antibodies (EmA) and correct genetics. Several studies have supported accuracy of the guidelines, but there are also conflicting results. These discrepancies could be caused by the use of error-prone histopathology as the diagnostic gold standard. We investigated accuracy of the guidelines by applying our validated standard operating procedures for quantitative duodenal morphometry.

Methods: The prospective multicenter study was conducted in clinical centres in Finland and Romania. Consecutive volunteers with celiac disease suspicion and positive TG2-Ab underwent blood sampling and gastroscopy with duodenal biopsies. TG2ab were measured by commercial ELISA (Celikey, Phadia) and EmA by indirect immunofluorescence. Routine histopathological analysis was done in clinical centres using grouped Marsh classification. Next, the biopsies were sent for centralized morphometric measurements including determination of villous height-crypt depth ratio (normal >2.0). Finally, accuracy of the positive ESPGHAN criteria for celiac disease was analyzed for both local and centralized results. In addition, children with low and high (>10x ULN) TG2ab underwent comparison of diagnostic characteristics. The study protocol and patient recruitment were approved by the Ethical Committees of all participant clinical centres. All participating children and/or their parents gave written informed consent.

Results: Altogether 164 seropositive children were enrolled. Their median age was 7.0 year and 71% were girls. One child was IgA deficient. Eighty-eight (54.0%) out of the remaining 163 cases had serum TG2ab ≥10x ULN. All 88 had positive EmA and right genotype required for ESPGHAN non-biopsy diagnosis. In local histopathological evaluation 87 (98.9%) of these children and 65 (86.7%) out of those 75 with TG2ab &LT; 10x ULN were found to have celiac disease. Centralized histology gave inconsistent result in one child positive for ESPGHAN criteria and in 11 with TG2ab &LT; 10x ULN. Thereafter, 100% of children with positive ESPGHAN criteria and 93% of those with TG2ab &LT; 10x ULN fulfilled either grouped or quantitative histopathologic criterion for celiac disease. Children with high TG2ab had significantly more anemia and less celiac disease in the family and higher median EmA and alanine aminotransferase values at diagnosis, whereas the groups did not differ in other laboratory values, demographic and anthropometric data, clinical presentation and presence of celiac disease-associated or other chronic conditions.

Conclusions: ESPGHAN non-biopsy strategy has 100% accuracy for celiac disease in children with a clinical suspicion when compared against optimized histopathological analysis. Small-bowel biopsy could be avoided with high accuracy in more than half of the children with celiac disease.

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Objectives and Study: Antibiotic-associated diarrhoea (AAD) is a common adverse reaction to antibiotics affecting 11-40% of children. AAD most frequently occurs 5 to 10 days after antibiotic treatment initiation, but might be observed even up to 8 weeks after the treatment. The aim of this trial was to evaluate whether lactoferrin might be used for AAD prevention. Human and bovine lactoferrin present destructive properties on most of etiological factors for AAD - Clostridium spp., Staphylococcus aureus, enteropathogenic and enteroadherent Escherichia coli (EPEC and EAEC), and Shigella spp; while it enhances Bifidobacteria proliferation.

Method: In this prospective, randomised, double blind, placebo-controlled, single-centre study we enrolled 156 children aged between 1 and 18 years, treated with antibiotic due to acute respiratory or urinary tract infection. The children were randomly allocated 1:1 to receive 100 mg of bovine lactoferrin or a placebo twice a day orally for the whole period of antibiotic therapy. Both lactoferrin and placebo sachets contained equal dose of maltodextrin. The primary outcome was the occurrence of antibiotic-associated diarrhoea during and up to two weeks after antibiotic therapy. Diarrhoea was defined as >3 stools a day, or a watery or loose stool with or without the occurrence of blood. Secondary endpoint was intravenous rehydration due to diarrhoea. The study protocol was approved by the bioethics committee and was registered on clinicaltrials.gov - NCT02626104.

Results: 156 children were enrolled into the study. Intention-to-treat analysis was performed. Antibiotic-associated diarrhoea occurred in 16 patients (21.3%) in bovine lactoferrin group and in 7 individuals (9.3%) in placebo group (OR 2.6 [95% CI 1.01 - 6.84] p 0.04). Relative risk was 2.29 (95%CI 0.89 to 5.88), number-needed-to-harm was 8.33 (95% CI 159.047 - 4.279). The need for intravenous rehydration occurred in 1 patient and there was no significant difference (p 0.3). No adverse effects were observed in both groups.

Conclusion: The trial indicated that bovine lactoferrin is not effective in AAD prevention. In contrast, the trial results showed that the risk for AAD was higher in bovine lactoferrin group as compared to placebo (group).
**Objectives and Study:** *Giardia lamblia* is a globally prevalent enteric protozoan parasite that is characterized by the myriad of clinical manifestations. This work was conducted to reveal the influence of host genetics on the susceptibility to *G. lamblia* infection and the variability in its clinical presentations.

**Methods:** A total of 80 children aged 2-16 years with giardiasis were enrolled, divided into symptomatic (n=40) and asymptomatic (n=40) groups. Another 20 Giardiasis free children with matched age and sex were included as controls. All included children were subjected to stool examination to detect *G. lamblia* and exclude other intestinal pathogens as well as human leukocyte antigen (HLA) class II alleles (DRB1) typing.

**Results:** The main gastrointestinal complaints among symptomatic giardiasis children were abdominal pain, diarrhea, flatulence, and vomiting in 95%, 47.5%, 40%, and 25%, respectively. The HLA-DRB1*03 allele was the most common allele shared in both symptomatic and asymptomatic giardiasis [32.5% and 36.25%, respectively], with (34.37%) overall frequency in children with *G. lamblia* infection; nearly 14 times as likely as the controls (2.5%); (OR, 40.7; 95% CI, 5.13-87.9; p&LT; 0.001). The second most common allele detected in giardiasis cases was HLA-DRB1*13 allele accounting for 16.25% in both symptomatic and asymptomatic cases, but was not a significant risk factor for *G. lamblia* infection (OR, 4.33; 95% CI, 0.86 -4.32; p= 0.084). On the contrary, HLA-DRB1*14 allele showed higher rates within the control group than among cases with giardiasis, estimating for 15% in controls and 3.75% in cases, giving a significant protective association with *G. lamblia* infection (OR, 0.19; 95% CI, 0.09 -0.79; p= 0.017). In addition, HLA-DRB1*04 allele prevalence was higher within the control group (20%) compared to giardiasis cases (10%), without being a significant protective factor (OR, 0.38; 95% CI, 0.12 -1.21; p= 0.66). Out of the 55 HLA-DRB1*03 alleles, HLA-DRB1*03:01 allele was the most frequent risky allele among children infected with giardiasis (44 alleles), and could serve as a significant risk factor for Giardiasis (OR, 27.06; 95% CI, 3.51-58.0; p&LT; 0.001). Also HLA-DRB1*03:01 allele was found to be predictive of symptomatic Giardiasis versus asymptomatic children with *G. lamblia* infection (*p*=0.012). On the contrary, HLA-DRB1*14:01 variant was the most common protective allele against *G. lamblia* infection (OR, 0.19; 95% CI, 0.04-0.79; *p*=0.005).

**Conclusion:** These results highlight that HLA class-II DRB1*03 alleles are likely to have an impact on human susceptibility to *G. lamblia* infection, while the HLA class-II DRB1*14:01 allele is probably involved in the establishment of host immune resistance against the disease.

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Phenotype, genetics and outcomes in an infantile-onset IBD cohort

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Objectives and Study: Very early onset inflammatory bowel disease (VEO-IBD) is a subtype of IBD in children less than six years old. Within this group, the rare subtype of infantile onset IBD (i.e. &LT; 2 years) comprises a unique group of patients with a growing number of monogenic disorders. We set out to characterize this group of patients and search for genetic causes of their disease.

Methods: In this prospective cohort study, children diagnosed with VEO-IBD were phenotyped and blood DNA was extracted for genetic testing. First, they were tested for mutations of interleukin 10 (IL-10) and IL-10 receptor A (IL-10RA) and B (IL-10RB) subunits. If no mutations were found, whole exome sequencing (WES) was performed to screen for 50 known VEO-IBD related mutations. We present here the results of 25 children diagnosed prior to 2 years of age tested between 2010-2017.

Results: Mean age at diagnosis was 10 months (range, 2-20 months). Median follow-up period was 4.9 years (IQR 7.0-2.1) Eleven had Crohn's-like disease, 3 had ulcerative-colicitis-like disease, and 11 had IBD-Unclassified. In terms of macroscopic involvement, the colon was affected in all patients, while 5 (20%) also had ileal disease. Five (20%) had upper gastrointestinal involvement and only 3 (12%) had perianal disease. Five (20%) had extraintestinal manifestations including sclerosing cholangitis, sacroilitis and arthritis.

Complete details on clinical course were available for 23 patients; these received multiple treatments including steroids (83%) antibiotics (57%) and nutritional therapy (30%) for induction treatment, thiopurines (70%) for maintenance therapy and mesalamine or sulfasalazine (65%), anti-TNF (52%), and methotrexate (22%) for induction and maintenance; 26% required surgery. Considering the entire cohort, at last follow-up 14 patients (56%) were in complete clinical remission, 5 (20%) had mildly active disease, 5 (20%) had uncontrolled disease including 1 lost to follow-up after 7 months and 1 (4%) died. Maintenance medication for the 14 patients who were in remission at last follow-up (n, %) included mesalamine or sulfasalazine (5, 20%), infliximab (3, 12%), methotrexate (2, 8%) and thiopurines (2, 8%). Of note, 3 (12%) were receiving no medical treatment including 1 who had had surgery.

Genetic analysis was completed for 21 patients. Plausibly related mutations were found in 5 (24%) patients: 1 had IL-10RA, NCF-1 and XIAP mutations, 1 had an IL-10RA mutation, 2 had MEFV mutations and 1 had an IKBKG mutation. Of note, the 2 IL-10RA mutations were deletions not detected by WES. One out of the 5 patients (IL-10RA mutation) died, and 2/5 (both with MEFV mutations) were treated surgically by colonic diversion, Only 1 patient in this group was in remission at last follow-up.

Conclusion: We have described the unique genotypic and phenotypic characteristics of a large prospective cohort of infantile-onset IBD patients. IL-10 genotyping and WES revealed monogenic disorders in 24%. While patients with monogenic disorders had a generally poor prognosis, the remainder actually had a 70% remission rate including 15% without maintenance medication. Genetic testing can differentiate between a monogenic disorder subset with often refractory disease and the remainder who have a generally favorable course.

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VEO-IBD consortium: interim report on genetic analysis of 480 patients and discovery of biallelic TGFB1 deficiency

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Objectives and Study: Very early onset inflammatory bowel diseases (VEO-IBD, onset &lt; 6 years of age) comprise a heterogeneous group of disorders clinically characterized by severe and often refractory intestinal inflammation. Paediatric IBD-like phenotypes have been associated with more than 50 monogenic diseases. Here, we present our experience on the genetic analysis of 480 patients from the VEO-IBD Consortium and report TGFB1 deficiency as novel cause for VEO-IBD.

Methods: To elucidate the molecular aetiology of VEO-IBD we conducted whole exome sequencing (WES). Immunological and biochemical assays were performed on peripheral blood mononuclear cells (PBMC), colonic lamina propria mononuclear cells (LPMC), and heterologous cellular models.

Results: Targeted and whole exome sequencing of 480 children with VEO-IBD and/or refractory paediatric IBD revealed monogenic disorders in 21 % of our patients (n = 100, 31 genetic entities). Our genetic screen identified biallelic TGFB1 mutations segregating with the disease phenotype in three patients from two unrelated pedigrees (P1: c.[328C>T];[1159T>C], p.[R110C];[C387R]; P2/P3: c.133C>T, p.R45C). The 10 years old index patient P1 presented with chronic active pancolitis accompanied by bloody diarrhoea and severe perianal disease in the first months of life. Similarly, P2 and P3 showed failure to thrive, bloody diarrhoea, and chronic colitis. All three patients had neurodevelopmental delay associated with epilepsy, brain atrophy, and/or posterior leukoencephalopathy. The siblings P2 and P3 died due to severe infections and multi-organ failure at the age of 2 and 3 years, respectively.

Immunophenotypical characterization of PBMC from patient P1 revealed a relative decrease of memory activated regulatory T (Treg) cells and an impaired T helper cell differentiation. CyTOF analysis of colonic LPMC showed decreased frequencies of FOXP3+ Treg, Th17, and CD103+ T cells. Moreover, we detected reduced T cell activation upon stimulation with anti-CD3/anti-CD28 and T cell proliferation in response to specific antigens in P1.

To validate the functional relevance of the identified mutations on TGF-β1-LAP biosynthesis and function we used heterologous HEK293T cells with lentiviral overexpression of wild-type and mutant TGF-β1. ELISA on supernatants from heterologous cells expressing mutant TGFB1 alleles showed reduced (R45C, R110C) or abrogated (C387R) secretion of the mature TGF-β1 growth factor as well as impaired stability of the TGF-β1-LAP small latent complex. SMAD-sensitive luciferase reporter assays demonstrated impaired TGF-β1-mediated downstream signalling activity in cells overexpressing mutant TGF-β1. Correspondingly, CyTOF analysis of LPMC isolated from colonic biopsies of P1 demonstrated a reduced in situ phosphorylation of SMAD2/3 in immune cells, indicating impaired bioavailability of mutant TGF-β1 for signal transduction.
Conclusion: Our study reports the first patients with biallelic loss-of-function mutations in \textit{TGFB1} and highlights the critical non-redundant role of TGF-\beta1 signalling in controlling human mucosal immunity and neurological development. Early genome-wide sequencing of patients with VEO-IBD is critical to establish molecular diagnosis and to identify novel therapeutic targets.
Activated phosphoinositide 3-kinase δ syndrome causes severe intestinal lympho-nodular hyperplasia and an IBD-like phenotype

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Objective: More than 50 different monogenic disorders causing intestinal inflammation have been identified in recent years. Activated phosphoinositide 3-kinase δ syndrome (APDS) is a recently described primary immunodeficiency resulting from PIK3CD and PIK3R1 mutations that manifests in the first years of life. Our aim was to characterize the gastrointestinal manifestations and immunological alterations of patients with APDS who presented with a severe IBD-like phenotype.

Methods: Detailed immune work-up was performed in three patients with APDS (two with PIK3CD mutation and one with PIK3R1 mutation) who presented with very early-onset IBD (VEOIBD). Whole exome sequencing was completed to identify pathogenic variants. In a single patient and two healthy controls paired blood and intestinal immune cells were analyzed by Mass CyTOF and high throughput sequencing of the T and B cell receptor gene segments.

Results: All patients manifested with recurrent sinopulmonary infections, bronchiectasis and splenomegaly, as well as chronic diarrhea due to severe intestinal lympho-nodular hyperplasia and an IBD-like phenotype in the first years of life. Two patients developed intestinal diffuse large B cell lymphomas in adulthood. Immune work-up displayed T cell lymphopenia and increased IgM levels. Whole exome sequencing identified deleterious genetic variants in PIK3CD or in PIK3R1. Mass CyTOF analysis showed a marked decrease in B cells in the intestine and blood accompanied with an increase in memory CD4 and CD8 T cells. Moreover, patient’s circulating CD4 and CD8 T cells produced very high quantities of IFNγ and TNFα. Finally, marked alterations in the T and B cell receptor repertoire patterns were observed in these patients with expansion of specific clones in both the blood and intestine.

Conclusions: APDS should be included in the differential diagnosis of VEOIBD, especially in patients with intestinal lympho-nodular hyperplasia. Given the profound proliferation in the gut and tendency to develop lymphomas these patients should be monitored closely. Novel PI3K inhibitors should be evaluated as a potential targeted therapeutic modality in these patients.

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Functional clustering of paediatric IBD patients: hypo-inflammatory immune signatures of innate signalling in a treatment naïve cohort

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Objectives and Study: Inflammatory bowel disease (IBD) is a cytokine-driven disease with an excess of pro-inflammatory mediators in the mucosa driving chronic inflammation. The aim of this study was to assess induced cytokine responses in paediatric patients with IBD, identify unique inflammatory signatures and stratify patients into immune functional groups based on cytokine responses through an unsupervised machine learning approach.

Method: Immune profiles of 12 ligand-induced cytokine responses were analysed in 22 treatment-naïve paediatric IBD patients at diagnosis and 10 paediatric controls to assess the functionality of key immune signalling pathways implicated in IBD including NOD2, IL-10 signalling, inflammasome activation and TLR signalling. Induced immune responses were analysed using peripheral blood mononuclear cells (PBMCs). Unsupervised machine learning algorithms were applied to the 12 domains of immune profiling (NOD2, TLR-2 & TLR-4 induced IL-10, IL-6, IL-1b and TNF-a) to stratify patients into functional immune clusters.

Results: The patient cohort showed a hypo-functional signature (p<0.0025) collectively across a panel of the 12 cytokine responses. Hypo-functionality was strongly driven by TLR-4-induced IL-10 (p=0.045), IL-1b (p=0.01) & TNF-a (p=0.018) and TLR-2-induced IL-10 (p=0.017) & IL-1b (p=0.015). No significant cohort signals for NOD2-mediated responses or signals for hyper-functionality were observed. Machine learning driven-hierarchical clustering stratified patients into 8 distinct clusters. Significant differences (p<0.05) were observed between clusters across one or more of the innate immune signalling domains.

Conclusion: The predominance of hypo-functional induction across multiple domains of innate immune signalling highlights inadequate cytokine responses and a consequent poor pathogen clearance as the key operating mechanism in the pathogenesis of IBD. This study represents a novel approach of adopting unsupervised machine learning to analyse induced cytokine responses in treatment-naïve paediatric IBD patients at diagnosis. The study provides a rationale for patient-stratification based on a machine-learning model of cytokine profiles to aid future diagnostics and therapeutics.

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**GASTROENTEROLOGY - Inflammatory bowel disease**

G-O-014

**Differences in therapeutic approaches and outcomes in paediatric and adult onset Crohn’s disease with Perianal fistula (CD-PAF): comparison of 2 multicentre fistula cohorts**

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**Objectives and Study:** While paediatric and adolescent onset CD is more severe disease with adverse outcomes, there is no comparative data on outcomes in perianal fistulae in paediatric/adolescent versus adult onset CD. Management paradigms in perianal fistulae in Crohn’s disease is not fully defined and approaches from paediatric and adult IBD clinicians and surgeons may be different. We aimed to study any differences in diagnostic and treatment approaches in paediatric/adolescent onset CD-PAF and adult onset disease and the outcomes of CD-PAF.

**Methods:** Data on patients included in 2 retrospective multicentre cohorts of perianal fistula with paediatric/adolescent onset and adult onset CD-PAF. We evaluated fistula characteristics, surgical and medical treatments following onset of CD-PAF and fistula healing. We also compared the need for re-intervention defined as the need for re-insertion of seton or abscess drainage or diverting stoma or proctectomy.

**Results:** 253 adults and 116 paediatric/adolescent patients were included. Complex fistula were identified in 53% of adult and 67% of paediatric/adolescent group. MRI was done at presentation in 77% and 73% respectively in adult and paediatric/adolescent group. Proctitis was recorded in 43% of adult onset and in 33% of paediatric/adolescent onset CD-PAF. Examination under anaesthesia (EUA) was done in similar proportion of patients (70% and 69%) but significantly higher proportion of adult CD-PAF patients had seton insertion (15% vs 54%, p<0.001). Anti TNF use was more often in paediatric onset CD-PAF (83% vs 68%) when compared to adult onset CD-PAF with majority of patients maintained on combination therapy. Complete clinical fistula healing was more often noted in paediatric/adolescent onset CD-PAF (71% vs 49%, p=0.015). Reintervention rates were higher in adult onset CD (40.3% vs 16.05%, p= &LT; 0.001). Radical surgery (diverting stoma or proctectomy) was required in 3 patients (2.58%) with paediatric/adolescent onset and 26 patients (10.28%) with adult onset CD-PAF (p=0.04).

**Conclusions:** Paediatric/adolescent onset CD-PAF appear to have better outcomes with less radical
surgery or re-interventions when compared to adult onset disease despite less frequent use of seton. The impact of more frequent and prolonged therapy in paediatric/Adolescent onset CD-PAF with combined immunomodulation needs further evaluation.

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Incidence and prevalence of UC, CD and their rare and severe complications; the first pan-European paediatric IBD database

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Objectives and Study: The incidence and prevalence of paediatric-onset inflammatory bowel disease (PIBD) and related complications is currently unknown or unclear in several European and non-European countries. We designed an electronic survey system, which allows us to collect PIBD denominator data, annually. With this study we aim to determine the incidence and prevalence of PIBD and its rare and severe disease or treatment related complications and reveal important differences between regions, populations and other variables as well as trends over time.

Method: An electronic survey system based on the Redcap database was designed to capture the referral and patient population of PIBD experts in 23 countries. This is part of the study examining rare complications of PIBD within the H2020 funded PIBD SETQuality. PIBD experts are invited to complete an annual survey that collects data regarding the location and type of clinical service, and number of new and current cases of PIBD. It also identifies from where their patients are mainly referred (regional coverage). A key element is the use of the Nomenclature of Territorial Units for Statistics (NUTS3) as defined by Eurostat.1 This structure allows us to combine the collected regional PIBD data with the 4600 validated datasets that are available in the Eurostat databases. In order to validate the quality of collected data, the source of information for entered data in each survey is also captured.

Results: Within one year we have gathered responses from 62 paediatric gastroenterologists in different regions of 16 European countries and Israel. The population covered reached 23.6 million children and so far we estimated incidence and prevalence for several regions using this system. For the United Kingdom (UK), the Netherlands (NL), Slovenia (SI), Italy (IT), Greece (GR) and Israel (IS), the coverage of the paediatric population reaches 54%, 77%, 100%, 35%, 66% and 57% respectively. The reported prevalence on country level spans from 17 in Italy to 49 patients per 105 children and adolescents in Sweden (Stockholm region only). Results for annual incidence of PIBD in several regions from 14 different countries are presented in Figure 1.
Conclusion: This has shown our ability to obtain incidence and prevalence data of PIBD, compatible with previous data, through studying a very large Pan European referral population allowing direct comparison between different countries and regions. These data will allow us to feed back precise figures to our responders in regard to their local populations and further examine reasons for reported differences in disease incidence and prevalence between countries and regions.

Disclosure of interest: This study was funded by Horizon 2020. Funding source number: 668023 PIBD-SETQuality.

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The gut microbiota composition and metabolic activity of HLA-B27 transgenic rats with gut inflammation resembles the dysbiotic characteristics of human inflammatory bowel disease

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Objectives and Study: Inflammatory Bowel Disease (IBD) is characterised by gut microbial dysbiois, in terms of bacterial composition and functionality. HLA-B27 (B27) transgenic rat is an established model of gut inflammation often employed to study human IBD. The extent to which the microbiota of this model resembles this of human IBD has not been reported in the literature. This study aimed to describe comprehensively the microbiota characteristics of B27 rats compared with their healthy HLA-B7 (B7) counterparts.

Method: Faecal samples of adult B27 and B7 rats (40-47 weeks) were collected the day prior to sacrifice. Caecal contents, caecal, ileal and colonic tissue and plasma were harvested at sacrifice. Intestinal inflammation was quantified by blinded histological scores. The relative expression (ΔΔCt) of tissue TNFα gene, plasma concentration of CCL-2 and faecal water content were measured. Short chain fatty acids in faeces and caecal content were measured with GC and microbiota composition was characterised using 16s rRNA gene sequencing. The concentration and total amount of bacteria in caecal content was measured with real-time qPCR.

Results: As expected B27 rats had higher inflammatory histology scores in ileum and colon, higher relative gene expression of caecal and colonic TNF-a, plasma CCL-2 and faecal water content (ΔMean, +2.3, +4.1, +6.6, +5.2, +44.9ng/ml, +15.7%, all p&LT; 0.05) compared to the B7 rats. The total caecal amount of butyrate, valerate, iso-butyrate and iso-valerate were significantly lower in B27 compared with B7 (ΔMean µmol, -89.5, -1.2, -0.9, -0.6, all p&LT; 0.05). Similarly, the faecal concentration of butyrate was significantly lower, while that of acetate and propionate significantly higher (ΔMean µmol/g stool, -9.7, +64.7, +3.4) in B27 than B7 rats. The total number of bacteria in caecal content (ΔMean, -0.4 log10 16S rRNA gene copies) was lower in B27 rats and their microbial community was characterised by a lower α-diversity (Chao and Shannon) than the B7 group (p&LT; 0.03). The microbiota structure (β-diversity) of B27 rats in faeces (p=0.04) and in caecal content (p=0.03) was distinct of that of the B7 rats, with the group effect explaining 42% of the variation. Out of 92 genera, the relative abundance of 42 (45.7%) was significantly different between the B27 and B7 groups in faeces. This was the case for 32 of the 104 (30.8%) genera in caecal content.

Conclusion: B27 transgenic rats present dysbiotic characteristics similar to human IBD, including the lower microbial diversity, the distinct microbiota structure and the reduced abundance of butyrate producing bacteria when compared to healthy status. This suggests that a monogenic cause of intestinal inflammation can drive microbial changes similar to those seen in human IBD.

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Objectives and Study: Ulcerative colitis (UC) and Crohn's disease (CD) are complex chronic disorders commonly known as inflammatory bowel disease (IBD). It is known that chronic or unresolved inflammation can result in an activated epithelial mesenchymal transition (EMT) that may lead to tissue destruction and fibrosis, both representing a common and severe complication in IBD patients. Specific molecular processes are engaged to initiate EMT, including the activation of several transcription factors. Recently, the zinc finger transcription factor ZNF281 (also known as ZBP-99 or ZNP-99) has been involved in EMT and cancer promotion in colorectal cancer (CRC). The aims of the present study are to investigate: 1) in vitro and ex vivo the expression levels of ZNF281 in intestinal inflammation and 2) in vitro the role of ZNF281 in EMT induced by inflammation.

Method: ZNF281 protein expression was analyzed by western blot in mucosal biopsies from inflamed and uninflamed colon of pediatric IBD patients (29 CD, 25 UC) and 16 healthy controls as well as in HT29 cells exposed to cytomix (TNFalpha+INFgamma) for 24 and 48 hours. ZNF281 mRNA was also analyzed in HT29 cells exposed to cytomix, by real-time PCR. Furthermore, ZNF281 was silenced and EMT (Snail, Timp1, ColA31, Slug) as well as inflammatory cytokine (IL8, IL17, IL23, IL1beta) genes were evaluated by real-time PCR.

Results: ZNF281 protein levels were significantly increased in inflamed colon of CD and UC patients as compared to uninflamed tissue of patients and controls (p<0.001). Similarly, ZNF281 protein and mRNA levels were significantly increased in HT29 cells exposed to cytomix compared to unexposed (p<0.05). Moreover, mRNA levels of Snail, Timp1, ColA31, Slug, IL8, IL17, IL23 and IL1beta were strongly decreased in ZNF281-silenced cells exposed to cytomix as compared to controls (cells treated with cytomix and scramble siRNA).

Conclusion: We show for the first time that zinc finger transcription factor ZNF281, previously known for its role in EMT, is importantly increased in gut inflammation and its deletion causes a fall in expression levels of EMT and inflammatory genes in inflamed cells. We suggest that ZNF281 may actively contribute to fibrosis development during IBD.

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Preterm birth, early nutrition and gut microbiota affect intestinal immunity via DNA methylation

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Objectives and Study: DNA methylation plays an important role for normal organ development and for adaptation to adverse conditions, resulting in altered gene transcription and cellular functions. Consequently, preterm birth and postnatal exposure to milk and microbes may affect intestinal development via DNA methylation. Using pigs as models for infants, we investigated the intestinal DNA methylome in response to shortened gestational age at birth, the first feeding and bacterial colonization, to understand how the immature intestine adapts to birth, diet and bacteria just after preterm delivery.

Method: The intestinal DNA methylome was characterized by reduced representation bisulfite sequencing of the middle small intestine from caesarean-delivered preterm or term pigs. In study 1, preterm or term pigs were euthanized shortly after birth or fed either total parenteral nutrition (TPN) or minimal enteral nutrition (MEN with bovine colostrum, COL) for five days. In study 2, preterm pigs were fed COL or infant formula (FOR) for five days. In study 3, preterm pigs were fed FOR for five days, with or without oral antibiotics to delay bacterial colonization.

Results: In study 1, the newborn preterm intestines showed genome-scale hypermethylation (relative to term), affecting genes related to innate immunity (LBP, lipopolysaccharide binding protein) and glucocorticoid signaling (NR3C1, glucocorticoid receptor). Promoter hypermethylation of LBP in preterm intestines down-regulated gene expression at birth and day 5, and it was associated with impaired LPS tolerance, regardless of feeding regimen (TPN or MEN). In study 2, FOR feeding increased intestinal LBP expression, relative to COL feeding, and increased bacterial epithelial adherence, complement protein (C3) and hypoxia-inducible factor 1-alpha (HIF1A). This was associated with LBP gene promoter hypomethylation. In study 3, antibiotics treatment reduced intestinal bacterial density, incidence of necrotizing enterocolitis ( NEC) and the expression of HIF1A and C3. These changes were associated with promoter hypomethylation of a C3 inhibitor.

Conclusion: Gestational age at birth (preterm or term), the first feeding and gut bacterial colonization induce intestinal DNA methylation changes. These changes may be associated with impaired or altered responsiveness to critical factors just after preterm birth (e.g. glucocorticoids, gram-negative bacteria), potentially explaining poor intestinal adaptation in preterm neonates. Even slow introduction of infant formula may induce bacterial dyscolonization and molecular changes that predispose preterm neonates to intestinal inflammation. Delaying bacterial colonization with antibiotics ameliorated intestinal inflammation and hypoxic stress, which may partly be mediated by DNA methylation changes. It remains to be investigated if the neonatal changes in intestinal DNA methylation have long term effects for intestinal development and health in preterm neonates.

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Lactobacillus reuteri cultured in green unicellular microalga Isochrysis rich in omega-3 provides a novel tool to limit AIEC growth and reduce gut inflammation

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Objectives and Study: Omega-3 and probiotics have been shown to induce favorable effects on a plethora of human inflammatory disorders, including inflammatory bowel disease (IBD). In this study, we provide in vitro evidence that the probiotic Lactobacillus reuteri (LR) can be grown in anaerobic condition in a monocellular algae medium, Isochrysis sp (IS), with high nutritional value for human nutrition, as it is rich in omega-3 fatty acids, and that this combination can counteract the growth of Escherichia coli adherent invasive strain (AIEC) LF82 and reduce gut inflammation.

Method: 1x10⁶ CFU of LR or 1x10⁷ CFU of LF82 AIEC were incubated, together or separately, in 36 gr/l of Isochrysis sp. in phosphate buffer solution (PBS) at 37°C for 5 days in anaerobic conditions. Sugars consumption, LR and LF82 growth were monitored to assess fermentation efficacy. Confluent CaCo2 were grown in DMEM and exposed to the fermented blend (LR+Is or LF82+Is or LR+LF82+Is) for 3 or 18 hours. Adhesion and Invasion assays were performed. Pro-inflammatory cytokines (IL-8 and TNF-a) were assessed by qPCR.

Results: LR grows in IS culture medium in anaerobiosis for 5 days (from 1x10⁶ to 1x10⁸). The growth of LR in IS is more efficient than that of LF82, despite the doubling time of LR is sensibly slower than LF82 (8h vs 30min) and the starting inoculum of the latter was 10 times higher (LR: 1x10⁶; LF82:1x10⁷). Moreover, LR cultured in IS, are more efficient to limit the adhesion and invasion of LF82 to CACO2 cells than LR or IS alone (LR+IS: adhesion reduced to 28.5±0.003% and invasion to 32.4±0.003%; LR: adhesion reduced to 65±0.001% and invasion to 75±0.001%; IS: adhesion reduced to 35±0.003% and invasion to 73±0.003%). Finally, the combination of LR and IS decreases, more than individually, the mRNA levels of pro-inflammatory cytokines, IL-8 and TNF-alpha, induced in CACO2 cells by exposure to LF82 (LR+IS vs LR: p<0.001; LR+IS vs IS: p<0.001).

Conclusion: We show for the first time that LR efficiently grows in anaerobiosis in a culture medium represented by the green microalga IS rich in omega-3. LR and IS together strongly limit the adhesion and invasion of AIEC bacteria as well as decrease the AIEC-induced inflammation in intestinal epithelial cells. This combination, due to the absence of side effects and the beneficial availability of both probiotic and omega-3 fatty acids, might be used for the treatment of intestinal inflammatory disorders, including IBD.

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Intestinal fetal organoids as a model of intrinsic postnatal epithelial maturation

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Objectives: One of the most important features of postnatal gut maturation in rodents is the change in intestinal brush border enzyme expression, allowing the epithelium to adapt from milk to solid food referred to as the suckling-to-weaning transition. Transplantation experiments of rodent fetal epithelium into subcutaneous tissue of adult animals suggest that at least part of this transition is intrinsically programmed and occurs in the absence of dietary or microbial signals. Mechanistic insight on gut maturation and how this process can be modulated is of pivotal importance for infants in whom the gut maturation process is delayed or compromised. In this context, we used mouse fetal intestinal organoids as a model and aimed to determine whether mouse fetal intestinal organoids in vitro mimic the in vivo gut epithelial maturation process that takes place from birth till weaning.

Method: Mouse intestinal organoids were cultured from primary fetal intestinal epithelial cells (E18-E19) for one month, with adult intestinal organoids cultured in parallel as control. Global gene expression profiles of fetal organoids at day 3 and day 28 of culture were identified by micro-array and compared to gene expression profiles of fetal and adult intestinal tissue. Subsequently, expression of specific maturation markers was evaluated weekly in fetal organoids by qPCR, enzyme activity assay and immunohistochemistry. To investigate whether gut maturation in fetal intestinal organoids can be modulated, organoids were treated with dexamethasone, a factor known to stimulate gut maturation.

Results: Global gene expression profiles showed an overall shift from fetal towards adult epithelium in fetal organoids cultured for 28 days, compared to day 3 of culture. Markers of neonatal intestinal epithelium (Argininosuccinate synthase 1, Blimp-1, Cnx43, FcRn and CRAMP) could be detected in fetal organoids at day 3, but were progressively lost in time and were completely absent at day 28 of culture as well as in adult control organoids. In contrast, markers characteristic for adult intestinal epithelium, such as sucrase-isomaltase, trehalase, arginase 2 and Paneth cell markers, were absent in the fetal organoids during the first two weeks of culture and gradually increased to adult levels after 4 weeks of culture. Results were confirmed on protein and enzyme activity level, indicating that the fetal organoids develop a functional adult brush border over time. Finally, dexamethasone accelerated certain aspects of in vitro maturation in fetal intestinal organoids (see Figure 1).
Conclusion: Our data show that mouse fetal intestinal organoids mature into adult epithelium in vitro, in a process that recapitulates the hallmarks of in vivo intestinal epithelial maturation. Fetal intestinal organoids can therefore be used to elucidate the molecular mechanisms of postnatal epithelial development and identify novel factors that influence the timing of epithelial maturation. Such insights are essential for a better understanding of (nutritional) factors that may promote gut maturation, especially for infants with delayed or compromised gut maturation such as preterm and undernourished infants.

Keywords: Intestinal epithelium, maturation, organoids

Disclosure of interest: I.R. and R.v.E. are employees of Nutricia Research. G.vd.B. is employee of GlaxoSmithKline. This project was financially supported by Nutricia Research.

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Prenatal endotoxin exposure induces postnatal systemic inflammation but does not increase diet-induced necrotizing enterocolitis in preterm pigs

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Objectives and Study: Prenatal inflammation is a major risk factor for preterm birth but it remains unclear how it affects the postnatal immune system and diet-induced gut inflammation. Using newborn preterm pigs as a model for preterm infants, we investigated the systemic immune status and the gut sensitivity to necrotizing enterocolitis (NEC) following fetal exposure to lipopolysaccharide (LPS) and after feeding different enteral milk diets just after preterm birth.

Method: At 103 d (88%) of gestation, fetal pigs received an intra-amniotic dose of LPS (1 mg/fetus, n=81) or control saline/no injection (CON, n=32). Preterm pigs were delivered by caesarean section three days later, euthanized immediately or fed for five days with formula (FORM, NEC-sensitive diet), bovine colostrum (COL, NEC-protective diet), or formula enriched with bovine milk caseinoglycomacropeptide (CGMP, CGMP-10, Arla Foods Ingredient, AFI) or osteopontin (OPN, OPN-10, AFI, n=10-15/group). Fetal membranes, amniotic fluids, blood and gut tissues were collected for analysis at birth and on day 5.

Results: At birth, intra-amniotic LPS induced histological chorioamnionitis, intra-amniotic inflammation (increased leukocyte counts and inflammatory cytokines) and a fetal systemic inflammatory response (increased cord blood neutrophils with impaired phagocytic function). On day 5, LPS pigs had systemic inflammation with elevated blood leukocytes and cytokines, and reduced serum albumin and cholesterol levels. At birth, the fetal intestine showed increased inflammatory cytokine levels and decreased villus height following LPS exposure, while LPS effects on gut parameters (cytokines, digestive functions, NEC sensitivity) were largely absent on day 5. COL feeding to LPS pigs reduced diarrhea incidence (40 vs. 91%), colon NEC (0 vs. 36%), gut inflammatory cytokines, and increased gut lactase activity, distal intestinal and colon goblet cell density and serum cholesterol and ion levels, relative to FORM. COL feeding to LPS pigs also reduced CD4+ expression in helper-T cells of mesenteric lymph nodes, and tended to increase blood T-helper cell frequencies and to decrease blood neutrophil phagocytic capacity, relative to FORM. CGMP and OPN supplementation to LPS pigs increased gut lactase activity and tended to reduce colon NEC incidence, relative to FORM. Neither CGMP nor OPN supplementation affected systemic immune parameters.

Conclusion: Fetal exposure to endotoxin predisposes preterm pigs to postnatal systemic inflammation but does not increase NEC sensitivity. Immunomodulatory milk diets may reduce gut inflammation in LPS-exposed preterm pigs but have limited short-term effects on systemic immunity. The postnatal milk diet is the most critical factor protecting preterm neonates from gut inflammation, regardless of exposure to endotoxin before birth.
[Figure 1: Experimental design]

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STAT6 variants interact with CYP2C19*17 to predict clinical outcome of proton pump inhibitor therapy in children with eosinophilic oesophagitis

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Objectives and Study: Recent guidelines support that Proton Pump Inhibitor (PPI) medications are a therapy for eosinophilic oesophagitis (EoE). Variants of signal transducer and activator of transcription 6 (STAT6) associate with EoE. STAT6 is the primary mediator of IL-4 and IL-13 signalling, and is responsible for transcriptional activation of CCL26 (eotaxin-3), which is up-regulated in EoE and is known to be a key mediator of eosinophil chemotaxis. CYP2C19 allelic variants influence the metabolism of PPI medications. In particular, CYP2C19*17 is a gain of function allele that confers a rapid or extensive PPI metabolizer phenotype. We hypothesized that genetic variants of STAT6 and CYP2C19 would associate with an EoE patient’s response to PPI therapy.

Method: Genomic DNA was isolated from 92 oesophageal tissue samples collected from a prospective clinical study of children using high dose PPI therapy (2 mg kg⁻¹ day⁻¹) to differentiate individuals with EoE responsive to PPI from individuals with EoE not responsive to PPI (Gutiérrez-Junquera C et al., JPGN, 2016). DNA was prepared from microtome sections of formalin-fixed paraffin-embedded tissue using a QIAamp DNA Tissue Kit. STAT6 single nucleotide polymorphisms (SNPs) (rs1059513, rs324015, rs3024974, rs841718, rs324011, rs167769, rs2598483, and rs12368672) were interrogated using TaqMan assays. Next, we identified CYP2C19 alleles with particular focus on *17 without compensating loss of function alleles (*1/*17, *17/*17).

Results: Of the 92 EoE patients, 57 (62%) were PPI responsive (PPIR) and 35 (38%) were not PPI responsive (PPINR).Table 1 compares the baseline characteristics between outcome groups. Wilcoxon rank-sum analysis showed that pre-PPI eosinophils/high power field (eos/hpf) were significantly elevated in non-responders relative to responders (mean count (SD): PPIR= 42(17); PPINR = 56(17), p = 0.030). Pre-PPI eos/hpf associated with STAT6 rs167769 (mean count (SD): major homozygote+heterozygote = 43(17); minor homozygote = 76(16), p = 0.007). Assuming a dominant genetic model with race, gender, age, dose and PPI type as covariates, STAT6 rs324011 and CYP2C19*17 were significant predictors of PPI therapy failure (>5 eos/hpf) in logistic regression models following correction for multiple testing (rs324011: OR = 6.12, 95%CI [1.63, 23.0], p = 0.037; *17: OR = 8.70, 95%CI [1.42, 53.2], p = 0.038) and significantly interacted with each other (OR = 0.114, 95%CI [0.0118, 1.11], p = 0.061). Focusing on a subsample of patients who were further characterized by pre-PPI pH probe analysis (n = 46), CYP2C19*17 carriers without loss of function alleles (*1/*17, *17/*17) were more likely to fail PPI therapy (OR 5.70, 95%CI [1.22, 26.72], p = 0.03).

Conclusion: Children with EoE who are carriers of STAT6 rs167769, rs324011 or CYP2C19*17 are less likely to respond to PPI therapy.
<table>
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<tr>
<th>Characteristic</th>
<th>PPIR (n=57)</th>
<th>PPINR (n=35)</th>
<th>p-value</th>
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<td>PPI dose mg·kg⁻¹·day⁻¹, mean(SD)</td>
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<td>Male, count(%)</td>
<td>41(71.9)</td>
<td>24(68.6)</td>
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<td>Age at diagnosis, mean(SD)</td>
<td>10.67(7.03)</td>
<td>10.78(7.04)</td>
<td>0.887</td>
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<td>Food allergies, count(%)</td>
<td>15(26.3)</td>
<td>9(25.7)</td>
<td>1.000</td>
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<tr>
<td>Dysphagia, count(%)</td>
<td>21(36.8)</td>
<td>17(48.6)</td>
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<tr>
<td>Impaction, count(%)</td>
<td>17(29.8)</td>
<td>16(45.7)</td>
<td>0.179</td>
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<tr>
<td>Eos/hpf, distal, mean(SD)</td>
<td>41.42(16.84)</td>
<td>55.85(17.15)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

[Table 1]

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**GASTROENTEROLOGY - Inflammatory bowel disease**

G-O-023

**Transmural healing evaluated by magnetic resonance enterography in paediatric Crohn's disease patients under maintenance treatment with biologics**

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**Objectives and Study:** Although, the currently acknowledged optimal treatment goal in Crohn's disease (CD) is mucosal healing (MH), transmural healing (TH) is emerging as a new goal, facilitated by the development of magnetic resonance enterography (MRE). We aimed to investigate TH and its relationship with MH in paediatric CD patients under maintenance treatment with biologics.

**Method:** This prospective study was conducted at the Department of Paediatrics, Samsung Medical Center from January, 2013 to June, 2017. Paediatric CD patients in whom ileocolonoscopies and MRE were performed simultaneously before starting treatment with biologics and at 1-year ± 2-years follow-up were included. MH was defined as a Simple Endoscopic Score for Crohn's disease (SES-CD) < 3. TH was defined as wall thickness ≤ 3 mm with the absence of ulcers, edema, enhancement, and complications on all ileocolonic segments evaluated by MRE. Factors associated with TH were investigated by logistic regression analysis. Cut-off points of Magnetic Resonance Index of Activity (MaRIA) scores for predicting MH and TH were also derived by receiver operating characteristic curve analysis.

**Results:** A total 72 patients (48 males, 24 females) were included in this study. The median age at diagnosis was 14.8 years (range: 7.5-18.6 years). At 1-year, MH and TH were achieved in 59.7% (43/72) and 22.3% (16/72) of the subjects, respectively. At 2-years, MH and TH were achieved in 66.7% (16/24) and 17.2% (4/24), respectively. All 20 patients who achieved TH at 1- or 2-years were under MH. SES-CD and MaRIA scores were each significantly lower in those who achieved TH compared to those who did not (SES-CD: median 0 vs. 3, \( P = 0.007 \); MaRIA: median 31.5 vs. 42.5, \( P < 0.001 \)). According to logistic regression analysis, MH at 1 year was the only factor associated with TH at 1 year (OR = 4.84, 95% CI = 1.39-22.72, \( P = 0.023 \)). The MaRIA cut-off point for predicting MH and TH was 52.1 (AUC = 0.772, 95% CI = 0.668-0.875, sensitivity 94.9%, specificity 52.8%, \( P < 0.001 \)), and 38.7 (AUC = 0.907, 95% CI = 0.86-0.955, sensitivity 90.5%, specificity 83.6%, \( P < 0.001 \)), respectively.
Conclusion: Approximately one-third of patients with MH are capable of achieving TH in paediatric patients under maintenance treatment with biologics. Although TH is a more stringent goal compared to MH, regular follow-up evaluation of transmural status by MRE and efforts to achieve TH may alter the natural course of CD in the era of treat-to-target.

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Viral infections as triggers of coeliac disease in a longitudinal birth cohort

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Objectives and Study: Viral infections have been suggested as possible environmental triggers of coeliac disease, but few prospective studies have been done. We aimed to test whether two common intestinal viruses, enterovirus or adenovirus, predicted coeliac disease.

Methods: During 2001-2007, a cohort of 46,939 Norwegian children was screened for the HLA genotype DR4-DQ8/DR3-DQ2 conferring an increased risk of coeliac disease and type 1 diabetes (the MIDIA study). The children identified with the risk genotype (2.2%) were followed with monthly stool samples from age 3 to 36 months and blood samples at age 3, 6, 9, and 12 months and then annually. During 2014-2016, 237 children consented to be screened for coeliac disease. All children without known coeliac disease were screened for IgA anti-tissue transglutaminase and IgG anti-deamidated gliadin peptide (EliA Celikey IgA/EliA GliadinDP IgG, Thermo Fischer Scientific, Phadia AB; Uppsala, Sweden). Thirteen children were diagnosed with coeliac disease according to the ESPGHAN guidelines, and in addition to 13 diagnosed before our screening, these 26 constituted the cases. For each case child, two children were randomly selected from the cohort with negative auto-antibodies, matched for duration of follow-up, date of birth and county of residence. We retrieved stored plasma samples for coeliac antibody testing using the same laboratory and assay as for the initial screening, to identify the seroconversion interval. For identification of enterovirus and adenovirus infections, we tested 2302 stool samples by quantitative real-time PCR methods. The association of virus with coeliac disease was primarily analyzed using a mixed effects logistic regression model with fecal sample virus positivity before seroconversion of coeliac disease antibodies as the dependent variables and case-control status as an independent variable. We adjusted for potential predictors of virus infection and/or coeliac disease; sex, age, age squared, season of sample collection, number of siblings, and family history of coeliac disease.

Results: Enterovirus was found in 385 of 2275 samples (17%). Enterovirus positivity was more frequent in samples collected prior to seroconversion for coeliac disease antibodies in cases compared to matched controls (adjusted odds ratio [aOR]: 1.42, 95% confidence interval [CI]: 1.04-1.95). Enterovirus infections during and after the seroconversion window were not associated with coeliac disease. In sensitivity analyses, long-lasting infections and infections with high virus load were also significantly associated with coeliac disease. In exploratory analyses, we found that enterovirus infections after gluten introduction and after end of breastfeeding were associated with coeliac disease while earlier infections were not. Enterovirus at the same time as reported fever was associated with coeliac disease, but other infectious symptoms were not. Adenovirus was found in 274 of 2140 samples (13%) with similar proportions among children who developed coeliac disease and control children.

Conclusion: This novel finding suggests that frequent enteroviruses may contribute to the etiology of coeliac disease. Further research is needed to confirm our results and should also be extended to other candidate viruses in larger sample sets.

Disclosure of interest: Thermo Fisher Scientific (Norway) has supported laboratory assays without charges. Supported by the Norwegian Coeliac Disease Association.

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Mucosal healing and histological remission in pediatric ulcerative colitis: does the target change the outcomes?

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Objectives and Study: Mucosal healing (MH) has emerged as a major therapeutic goal in ulcerative colitis (UC). Whether it should be the ultimate therapeutic target is already unknown. In fact, recent data suggest moving forward to the concept of "complete remission", including histological healing as a predictor of better outcomes than mucosal healing alone. Thus, we aimed at investigating long-term outcomes in pediatric patients with complete remission compared to those with endoscopic MH alone.

Method: Blinded evaluation of endoscopic and histological findings was performed in children with a known diagnosis with UC at baseline. MH was defined as a Mayo score ≤1, while histological remission as a grade 1 (no significant inflammation) based on Truelove and Richards' index. Complete remission was defined as MH + histological remission. Pediatric ulcerative colitis activity index (PUCAI) was used to evaluate clinical relapses (PUCAI>35). C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and albumin were evaluated at baseline, 6, 12 and 24 months. Corticosteroid use, clinical relapse, hospitalization, treatment escalation, disease extension and colectomy rates were determined over a 2-year follow-up.

Results: Forty-eight patients with UC and MH at baseline (median age 8, IQR 1.75-18 years, females 52%) were followed up for a median of 29 months (IQR 12-93 months). Twenty-six patients (52%) had complete remission, 23 (48%) had a residual histological mild-moderate inflammation. No patient had severe inflammation. At 6-month follow-up, a significant difference of CRP, ESR, and albumin was found between patients with complete remission and mucosal healing (p=0.004, p=0.0002, p=0.012 respectively); this difference remained significant for albumin at the subsequent follow-up (p=0.006 at 24 months). Histological remission did not predict any of the patient clinical outcomes evaluated (corticosteroid use, clinical relapse, hospitalization, surgery, disease extension, and treatment escalation) over the 2-year follow-up.

Conclusion: Histological remission doesn't seem to predict better clinical outcomes than MH in pediatric UC. Further data are required before considering complete remission as a treatment goal of pediatric UC.

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Cystic fibrosis dyslipidemia revisited: a prospective, cross-sectional study

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Objectives and Study: Longer survival of patients with cystic fibrosis (CF) draws attention to their risk of cardiovascular disease, which might be increased by CF dyslipidemia: hypocholesterolemia, hypertriglyceridemia, and insufficient high-density lipoprotein cholesterol (HDL-C). Previous research on CF dyslipidemia did not include a direct comparison with healthy subjects (HS); multivariable analyses are also lacking. Furthermore, the ratio of oxidized low-density lipoprotein (oxLDL) to LDL cholesterol (LDL-C) and serum apolipoprotein E (ApoE) levels have not been studied in CF to date.

Methods: The following were measured in the serum: total cholesterol, LDL-C, HDL-C, triglyceride (Trinder method), oxLDL, adiponectin, and ApoE concentrations (ELISA). The assessed clinical characteristics included: body mass index (BMI), exocrine pancreatic insufficiency (fecal elastase-1, ELISA), forced expiratory volume in 1 second (FEV1%), the presence of CF-related liver disease, and Pseudomonas aeruginosa colonization. CFTR mutations were classified as severe i.e., type I and II, or other, including unknown.

Results: The study comprised 108 CF patients and 51 HS of similar age and sex. The median FEV1% in the CF group was 61% [1st-3rd quartile: 46-84%]. Compared with HS, in CF the following odds ratios were found for abnormal lipid concentrations: hypercholesterolemia > 190 mg/dL OR = 0.37 (95%CI 0.15-0.91), LDL-C ≥ 100 mg/dL OR = 0.30 (95%CI 0.13-0.65), HDL-C ≤ 45 mg/dL OR = 13.29 (95%CI 3.90-45.30), hypertriglyceridemia ≥ 150 mg/dL OR = 3.18 (95%CI 1.04-9.74). These disturbances concerned the following fractions of the CF population: hypercholesterolemia 10%, high LDL-C 14%, low HDL-C 45%, hypertriglyceridemia 21%. While hypocholesterolemia &LT; 115 mg/dL occurred in 31% of CF patients, it was found in no HS (Fisher’s exact p &LT; 10^-4). Hypocholesterolemia was more common in pancreatic-insufficient compared with pancreatic-sufficient CF patients (OR = 11.40; 95%CI 1.46-89.15); high LDL-C levels occurred less often (OR = 0.15; 95%CI 0.04-0.42). Among the pancreatic-sufficient CF patients 40% (n = 8/20) had elevated LDL-C and 20% hypercholesterolemia. In multivariable analyses, total cholesterol was higher in males and increased with age (independent associations). LDL-C was lower in patients with exocrine pancreatic insufficiency and was higher in subjects with higher BMI. Non-HDL-C was lower in exocrine pancreatic-insufficient participants, but higher in females and those with higher BMI. HDL-C was lower when a severe CFTR genotype was present; it increased with age. Adiponectin was lower in CF subjects with higher BMI. Other characteristics of the disease - including FEV1% - did not predict the investigated lipids. OxLDL/LDL-C ratio, adiponectin, and ApoE concentrations did not differ between CF patients and HS. The clinical characteristics did not independently associate with oxLDL/LDL-C ratio or ApoE concentrations.

Conclusion: Dyslipidemia is highly prevalent in CF patients. A considerable fraction of pancreatic-sufficient CF patients have hypercholesterolemia. OxLDL/LDL-C ratio and serum concentrations of adiponectin and ApoE do not seem to play an important role in CF-associated lipid disturbances.

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Development of the Pediatric Inflammatory Crohn’s MRE Index (PICMI) - results from the ImageKids Study

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Objectives and Study: There is no validated MRE-based inflammatory index for children although Crohn's disease (CD) is more often panenteric compared to adults. The aim of the multicenter prospective ImageKids study was to develop such an index termed Pediatric Inflammatory Crohn’s disease MRE Index (PICMI).

Method: 158 children with CD (age 14±2.4 years, 54% males, median disease duration (2.1 (IQR 0.3-4.3) years) underwent an MRE and ileocolonoscopy along with extensive collection of clinical data including SESCD and wPCDAI and bio-sampling in 21 sites globally. All MREs were scored independently by the site radiologist and by two central radiologists; the bowel was divided into 20cm segments and sections (jejunum, ileum TI and colon). Measured variables included length of involved segments, a radiologist global assessment of inflammation on a 0-100mm visual analog score (VAS) and 9 items selected by a Delphi group of 30 international radiologists and a systematic review of the literature (reported separately): wall thickness, T2 intensity, enhancement, DWI, narrowed lumen, comb sign, ulcerations, vascular engorgement and motility as well as the adult MaRIA score.

Results: 368 involved bowel segments were scored in 158 enrolled children. Based on univariate analyses, the following items were selected for the PICMI Index: wall thickness, T2 intensity, DWI, narrowed lumen, comb sign, ulcerations, and mesenteric T2 intensity (all P< 0.001; Figure1). In an attempt to avoid gadolinium exposure in children, mucosal and mesenteric enhancement were not selected but will be evaluated further in the validation stage. Linear regression was used to determine the weights of scoring between bowel sections. The radiologist assessment was found to be well predicted by linear regression on the index variables. The models showed satisfying linear fit; for some sections retained only some of the variables (jejunum R² =0.80, ileum R² =0.30, TI R² =0.41; all p< 0.0001)
[Figure 1]

**Conclusion:** The PICMI index is being developed as a MRE tool for pediatric CD to supplement endoscopic assessment. The draft weighted PICMI will be now validated on a separate cohort and compared with the MaRIA.

The ImageKids study is funded by an educational grant from Abbvie

**Disclosure of interest:** Last 3 years DT received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, AstraZeneca, Abbvie, Takeda, Boehringer Ingelheim, Biogen, Atlantic Health, Shire, Celgene, Lilly

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Profoundly increased mortality in patients with CF related cirrhosis

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Objectives and Study: Between 2 and 10% of patients with Cystic Fibrosis develop CF related cirrhosis (CFC). The lifetime impact of CFC on mortality has so far not been quantified. The availability of a national registry on CF care and relevant outcomes offers a unique opportunity to assess the mortality risk of CF patients with or without CFC. We aimed to determine the role of CFC on CF patient survival based on national data of the Netherlands.

Methods: We identified all CFC patients in the Netherlands who had been alive at 1-1-2009, based on the review of medical records. CFC was defined either by ultrasound demonstration of the combination of inhomogeneous liver parenchyma and splenomegaly, or by the histological diagnosis. A control group was obtained from the national CF registry, consisting of 980 CF patients without CFC. We compared the groups with regard to survival and age at death, in the period 1-1-2009 to 31-12-2014. In case of mortality in either of the two groups, the primary cause of death was retrieved from the medical records.

Results: We identified 103 CF patients with CFC and 980 CF patients without CFC at the start of the study period. In the subsequent 6 years, compared to the control group, the mortality rate was significantly higher in CFC patients (22/103, 21%) than in non-CFC controls (63/970, 6%; P&LT; 0.01). The median age of death was 10 years lower in CFC than in non-CFC patients (27 vs. 37 years, resp.; P=0.01). A significantly higher proportion of CFC patients died before the age of 25 years, compared to the control group (45% vs. 27%; P&LT; 0.01). At the start of the study period, CFC and non-CFC patients did not significantly differ in pulmonary function tests (forced expiratory volume at 1 s; % of predicted forced vital capacity), nor in body weight or body mass index, indicating similar clinical conditions at that moment. In the diseased CFC patients, the cause of death had been attributed to pulmonary disease in the 68% of the cases, and to chronic or acute-on-chronic liver failure in 18%, several times subsequent to an elective surgical procedure.

Conclusion: Our national data compellingly demonstrate that CFC is a critical risk factor for early mortality in CF patients and suggest that CFC has a negative effect on life expectancy of 10 years. The mortality seems either due to a strongly accelerated decline in pulmonary function or to liver failure, for example after an elective surgical procedure. A more detailed identification of CFC patients who have the highest risk of mortality seems now indicated for the consideration of preemptive liver transplantation.


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Retrospective analysis of pharmacokinetic Infliximab data in young IBD patients at the age of 9 or younger

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Objectives and Study: Infliximab (IFX) is administered intravenously in a weight-based dose (5 mg/kg) in pediatric and adult Inflammatory Bowel Disease (IBD) patients. However, previous IFX pharmacokinetic (PK) data suggest this results in lower mean serum IFX concentrations in pediatric compared to adult CD patients, especially in young patients. The hypothesis is that children need a more intensive treatment regime than the current weight-based dose administered.

Aim: To assess IFX PK, based on existing therapeutic drug monitoring (TDM) data in a population of pediatric IBD patients age 9 years and younger.

Method: TDM data were retrospectively collected in 15 centres. Children treated with IFX between 2004-2016 were included, if IFX was started as IBD treatment at the age of 9 years or younger and PK/pharmacodynamics data were available.

Results: Data of 1488 IFX infusions and 647 trough levels were collected from 112 children (median start age for IFX: 8.29 years (0.82-9.98), 60 males, 66 with Crohn disease (CD), 33 with Ulcerative Colitis and 13 with IBD-Unclassified. Twelve percent (n=13) of children showed a primary non response (lack of improvement of clinical signs and symptoms after induction therapy) on IFX treatment. During follow up (median 435 days (26-2641), 59% (n=66)) of patients received increased IFX dose during treatment. The median dose at start was 5.0 (4-11) mg/kg; at the end of follow up (n=79) this was significantly raised to 8.0 mg/kg (4-12); p&LT; 0.001. In 70% (n=78) of the children the interval of the infusions was shortened. In 17% (n=19) no intensification, loss of response or interval adjustment occurred during follow up. We found no significant difference in dose, need for dose intensification, loss of response, or need of interval adjustment between the children with very early onset CD (n=16, start IFX < 6 of age) and early onset (n=96 start IFX between 6-9 years). Thirty-five percent (n=228) of the 646 (median level 4.5 (0-99) trough levels were measured in the therapeutic range of 3-7 mg/L. Respectively, 34% (n=221) of the trough levels were measured below the 3 mg/L and 31% (n=201) were above 7 mg/L. In children below 25kg (n=250) the median trough level was 3.80 (0-45) this was significant lower (p=0.001) compared to the levels of children above 25kg (n=378, median 5.0 (0-99)).

During follow up antibodies to infliximab (ATT’s) were measured 721 times in total. In 37% (n=41/112) of the children the ATT’s turned positive during follow up; this resulted in a secondary loss of response (loss of response during maintenance treatment, after successful induction of symptoms) in 25% (n=28) of the patients. During follow up 54 Adverse Events (AE) and 1 Serious Adverse Events (SAE)
were reported. The SAE reported was death of the child, which was not related to the use of IFX. In 5% (n=6) of cases IFX was stopped because of an Adverse Event (EA).

**Conclusion:** Taken together, the results of this study show IFX doses of 5 mg/kg weight-based dose given in interval of 8 weeks after induction for a majority of the children was an insufficient treatment strategy. Doses of IFX were significantly increased between start and end of follow up. Moreover, our results show significant lower trough levels measured in children below 25kg compared to children above 25kg.

**Disclosure of interest:** L. de Ridder: the author collaborate with Shire, Nestlé, Merck, Janssen biologics, Abbvie and Pfizer/Hospira for industry sponsored studies, investigator initiated studies and consultancy. The author also receives a grant from ZonMw.

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Evaluation of adalimumab effectiveness in paediatric patients with ulcerative colitis in clinical practice

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Objectives and Study: Adalimumab (ADA) is an anti-tumor necrosis factor agent approved for the treatment of ulcerative colitis (UC) in adults. We assessed the duration and effectiveness of ADA in paediatric UC patients in clinical practice.

Methods: In a retrospective cohort study using registry data from 47 centers in the USA in the ImproveCareNow network, patients with UC treated with ADA prior to 18 years old with at least one follow up visit were identified. Clinical care and frequency of visits were decided by the patient, parent, and clinician. Data from clinical care visits were assessed every 3 ± 1.5 months for 1 year, then every 6 ± 3 months through 3 years. If a patient had no visit during that period but was still active in the registry, the result from the previous visit was carried forward (for up to 9 months). The analysis population consisted of patients still on ADA at the respective visit after imputation. Patients’ data were excluded from analyses after a colectomy. Steroid-free clinical remission rates, per Physician Global Assessment (PGA, inactive) and Pediatric Ulcerative Colitis Activity Index (PUCAI, < 10), and steroid free clinical response rates, per PGA (inactive or mild) and PUCAI (< 35), were assessed. The absence of abdominal pain and bloody stools was also assessed. Descriptive statistics, Kaplan-Meier analysis for colectomy rate, and Fisher’s Exact Test for associations between concomitant therapy and outcomes were performed.

Results: 133 UC patients (24% < 13 years old at therapy onset; 58% female) received ADA between August 2008 - November 2016. At months 3, 6, 12, 24 and 36 post-initiation, 130, 119, 76, 34 and 16 patients were followed; 89%, 78%, 80%, 97% and 75% of followed patients remained on ADA. Of patients on ADA at 3, 6, 12, 24 and 36 months: 37%, 57%, 68%, 71% and 73% were in steroid-free clinical remission by PGA; and 30%, 45%, 63%, 68% and 82% by PUCAI. Of patients on ADA at 3, 6, 12, 24 and 36 months: 59%, 70%, 85%, 87% and 91% were in steroid-free clinical response by PGA; and 60%, 74%, 81%, 87%, and 82% by PUCAI. Of patients on ADA at 3, 6, 12, 24 and 36 months: 38%, 52%, 68%, 68%, and 64% reported the absence of abdominal pain and bloody stool.
The probability of remaining colectomy-free at 3, 6, 12, 24 and 36 months was 97%, 94%, 86%, 80% and 70%. 14 hospitalizations occurred in 8 patients, and 5 serious infections occurred in 5 patients. Concomitant immunomodulator therapy did not appear to improve outcomes.

**Conclusion:** Durable rates of steroid-free remission were observed in paediatric patients with UC on ADA in routine practice. Of patients followed for 24 months, 97% of patients remained on ADA and approximately 70% of patients were in steroid-free clinical remission. 80% of patients remained colectomy-free for 24 months.

**Disclosure of interest:** Brad Pasternak: Speaker for AbbVie Andreas Lazar: Employee and Shareholder of AbbVie Mareike Bereswill: Employee and Shareholder of AbbVie Anne Robinson: Employee and Shareholder of AbbVie Richard Colletti: Consultant for AbbVie, Jannsen Biotech, Accordant Health Services; Scientific Advisory Board: Jannsen Biotech, Accordant Health Services ImproveCareNow: Funding for study provided by AbbVie

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Efficacy of Adalimumab as first-line “top-down” therapy in pediatric Crohn's Disease: 12 months of follow-up

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Objectives and Study: Anti-tumour necrosis factor (TNF) agents are highly efficient in inducing and maintaining remission in pediatric Crohn's disease (CD). The question is who is the right patient and when is the right moment to introduce anti-TNF medication. Recent ECCO-ESPGHAN guidelines indicate a clear place of anti-TNF biologics in patients with positive predictors of poor outcome. The aim of our study was to evaluate the efficacy of adalimumab (ADA) as first-line therapy by comparing two different strategies: ADA “top down” in immunomodulator and anti-TNF naïve CD patients versus a “step up” strategy in patients receiving immunosuppressive agents (thiopurine and/or infliximab) before ADA.

Method: Patients followed for CD at Necker hospital that started their ADA therapy between 2005 and 2017 were retrospectively reviewed. The beginning of the study (M0) was the date of first ADA injection. Enrolled patients were divided into 2 groups according to the treatment strategy. Group A was composed of patients naïve of immunosuppressors and anti TNF agents who started early ADA after induction of remission, resulting in a “top down” strategy while group B was composed of patients who started ADA after a more classical strategy (ie “step up” strategy using immunosuppressive agents then infliximab). For each patient were collected data at M0, M3, M6, M9 and M12 regarding the disease activity score (wPCDAI), auxological parameters, biological parameters (CRP, ESR, Albumin, ADA trough levels and antibodies anti-ADA).

Results: 83 patients (43 boys) were enrolled in the study, 43,3% (n=36) in group A and 56,6% (n=47) in group B. Mean age at the start of ADA was 13.6 ± 2.6 years. At inclusion the 2 groups were comparable with a mean wPCDAI of 40.75 ± 14,8 in group A versus 45.6 ± 15,5 in group B. At 6 months, the 2 groups were in clinical remission with a median wPCDAI of 0 (0-12.5 IQR) in group A (n = 30) versus 0 (0-7.5 IQR) in group B (n=38) (p: 0.509). CRP level decreased from 15.5 (4.7-35.8 IQR) to 1.1 (0.5-5.6 IQR) in group A vs 17.1 (6.5-37.7 IQR) to 4.8 (0.7-6.1 IQR) in group B (p: 0.945 et p: 0.086). For the subgroup of patients who reached the 1 year follow up, there were no significant differences regarding the mean wPCDAI, CRP, ESR and serum albumin between the 2 groups.

Conclusion: The present study demonstrates that the “top down” strategy using early ADA monotherapy in disease course is as effective as a step-up strategy. Moreover, ADA monotherapy is as effective as combottherapy in maintaining clinical and biological remission at 1 year of follow-up in paediatric CD patients. Those results are very important to identify the best strategy in pediatric CD patients, where safety concerns are major.

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GASTROENTEROLOGY - Inflammatory bowel disease

G-O-032

Impact of changing treatment strategies on outcomes in paediatric Ulcerative Colitis

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Objectives and Study: Management strategies and therapeutic goals for children with Ulcerative colitis (UC) have changed in recent years. The concept of composite or deep remission emerged; early use of immunomodulators was incorporated into guidelines; and biological therapies became available.

Our aim was to evaluate the change in outcomes: (1) colectomy rate; (2) disease flares per year; and (3) number of hospital admissions in children with UC managed at a tertiary gastroenterology centre over the past twelve years.

Method: Retrospective analysis of children diagnosed with UC under care at the Royal Children's Hospital, Melbourne between 2005-2010 (Group 1) or 2011-2016 (Group 2). The time period was divided based on the year of approval by the Australian Therapeutic Good Administration for the use of a TNFa antagonist (Infliximab) for moderate to severe paediatric UC. Colectomy rates were compared between groups using a Kaplan-Meier survival analyses accounting for differences in follow-up. 'Early' colectomy was defined as children undergoing colectomy within 6 months from diagnosis of UC.

Results: 204 children (102:M) with a median age at diagnosis of 12 (IQR 5) years were diagnosed with UC over the study period. Group 1 had 71 children [35 M, age 12(IQR 8) years] and Group 2 133 children [67 M, age 13(IQR 4) years]. Groups 1 and 2 had comparable baseline disease severity with respect to disease distribution (pan colitis) [Group 1 - 57% vs. Group 2 - 69%, p = 0.28] and Mayo Endoscopic Sub-Score (Mayo3) [Group 1 - 31% vs. Group 2 - 35%, p = 0.76]. The use of TNFa antagonists increased from 4.2% (3/71) to 13.5% (18/133) between Group 1 and 2, respectively. TNFa antagonists were utilised earlier in treatment in Group 1, 11 (IQR 7) months vs. 38 (IQR 40) months, p = .001 in Group 2. The proportion of patients treated with systemic corticosteroids, 5-aminosalicylic acid, azathioprine and tacrolimus was similar between eras. Sixteen patients (12 - Group 1; 4 - Group 2) underwent colectomy. The 5-year cumulative probability of colectomy decreased from 24% to 6% (p = 0.01) between the first and second era (Figure 1). This decrease was observed in both early and late colectomies. There was no change in the median number of flares per year [Group 1 - 0.41 (IQR 0.6) vs. Group 2 - 0.62 (IQR 0.91), p = 0.28] or median number of hospital admissions per year [Group 1 - 0.30 (IQR 0.77) vs. Group 2 - 0.21 (IQR 0.75), p = 0.52].

Conclusion: A reduction in colectomy rates has been observed in Australian children with Ulcerative Colitis. The frequency of disease flares and hospital admissions remains unchanged.
Figure 1. Cumulative risk of colectomy in pediatric UC patients in Group 1 (2005-2010) and Group 2 (2011-2016)

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Manipulating the microbiome in pediatric Acute Severe Colitis with antibiotics cocktail: a randomized controlled trial

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Objectives and Study: A previous case series suggested a benefit of antibiotic-cocktail in steroid-refractory paediatric UC. In this pilot randomized investigator-blinded controlled trial we aimed to evaluate the effectiveness of wide-spectrum antibiotic regimens in acute severe colitis (ASC) in addition to standard intravenous corticosteroid (IVCS) therapy.

Method: Children 2-18 years with ASC (i.e. PUCAI>=65) were randomized into two arms: the first received antibiotics in addition to IVCS (amoxicillin, vancomycin, metronidazole, doxycyclin (or ciprofloxacin in those younger than 8 years of age)-AB+IVCS), while the other received only IVCS. Children with proctitis, infections, and those treated with antibiotics in the preceding 4 weeks were excluded. The primary outcome was the total PUCAI score at day 5 of treatment. Missing data for ITT analysis were imputed using the NRI method for categorical variables and LOCF for continuous variables.

Results: 30 children were randomized and 2 were excluded (one positive for CMV and one salmonella): 16 in the AB+IVCS and 12 in the IVCS arms (mean age 14±2.7 years, range 7-18, 15 (54%) males, 23 (82%) extensive colitis). Baseline variables were similar between groups (PUCAI 73.1±6.6 vs. 75±7.1, respectively). The mean day 5 PUCAI was 25±16.7 vs 40.4±20.4, respectively (p=0.037).
Bearing in mind that the trial was not powered for this, there were no differences in the need for 2nd line therapy during the admission nor in the colectomy rate 1 year following admission (both 3/16 (19%) vs. 2/12 (17%)). Median admission days (IQR) was also similar (7.5 (5-10) vs 9 (5.5-13); p=0.35). Microbiome analysis upon admission was available for 22 children of whom 8 (36%) had a predominant bacteria (>33% abundance).

**Conclusion:** In this first RCT ever performed in children with ASC, an antibiotic cocktail in addition to IVCS improved disease activity on day 5. Further and larger studies are needed to determine whether this is associated with improved long term hard outcomes.

**Disclosure of interest:** This study has been funded by Helmsley Charity Trust and IOIBD

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GASTROENTEROLOGY - Inflammatory bowel disease

G-O-034

Cmorbidities in adolescents with inflammatory bowel disease: findings from a population-based cohort

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Objectives and Study: Inflammatory bowel diseases (IBD) are systemic inflammatory conditions associated with various autoimmune disorders and higher prevalence of other diagnoses and complications. We aimed to investigate the association of IBD with various medical conditions at late adolescence in a large cross-sectional population-based study.

Methods: A total of 1,142,732 Jewish Israeli adolescents who underwent a general health examination at a median age of 17.1 years from 2002 to 2016 were included. A definite diagnosis of IBD was based on accepted criteria. Cases were further classified into Crohn's disease (CD) and ulcerative colitis (UC). Covariate data included demographic measures, and data on associated medical conditions.

Results: Overall, data for 891 subjects with IBD (595 with CD, 296 with UC) and 1,141,841 controls were available.
Multivariate analyses showed that autoimmune diseases were significantly more common in subjects with CD, including primary sclerosing cholangitis (PSC), odds ratio (OR 354), autoimmune hepatitis (OR 4), arthritis (OR 3), thyroid diseases, and uveitis (OR 4.7). Positive correlation in multivariate analysis was observed in UC for PSC (OR 1131), autoimmune hepatitis (OR 3.4), arthritis (OR 2.4) and immune thrombocytopenic purpura (OR 5.9), p<0.001 for all positive associations. Asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, chronic urticaria, vasculitis, thyroid diseases, and vitiligo were not associated with either CD or UC.
Non-autoimmune associations for CD included urolithiasis (OR 3.6), pancreatitis (OR 21.5), and renal diseases (OR 2.7), p<0.001 for all. UC was associated with pancreatitis (OR 26.1), and urinary abnormalities (OR 3.2), p<0.001 for all. Interestingly, fractures of long bones were negatively associated with both CD (OR 0.51) and UC (OR 0.67). Axial fractures and migrane were not more common in both CD and UC. All positive associations were more prevalent in male patients with either CD or UC. Celiac disease was only associated with diagnosis of CD in males (OR 3.7).

Conclusion: Already at adolescence, both CD and UC are associated with multiple comorbidities, not limited to autoimmune disorders. There is a male preponderance for most comorbidities.

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Improvements in medical treatment and surgical outcome of children and adolescents with ulcerative colitis in the United Kingdom

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16St George’s Hospital, London, United Kingdom
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Objectives and Study: Children with ulcerative colitis are affected by steroid dependency, anaemia, and complications of surgery. To improve these nationwide, we examined the efficacy of steroid sparing strategies and surgical outcomes by a coordinated approach to all national leads for inflammatory bowel disease. We examined morbidity and escalation treatment for children with active UC, steroid sparing strategies, proportion of second line treatment and surgical outcome, highlighting geographical differences, areas of improving practice and areas for future development.

Method: The 4th round of our national prospective audit was conducted for the inpatient period of all children with ulcerative colitis for medical or surgical treatment in the UK from 1.1.-31.12.2013. Of 34 centres invited 32 participated and recruited 224 children in 298 admissions. We compared results with two previous paediatric audit rounds.

Results: Over six years, recording of PUCAI score (median 65)(23% to 55%, p<0.001), guidelines for acute severe colitis (43% to 77%, p 0.04), and ileal pouch surgery registration (4% to 56%, p<0.001) have increased. Corticosteroids were given in 183/298 episodes (61%) with 61/183 (33%) not responding and requiring second line therapy or surgery. Of those treated with anti-TNFalpha (16/61, 26%), 3/16 (18.8%) failed to respond and required colectomy. Prescription of rescue therapy (26% to 49%, p=0.04) and proportion of anti-TNFalpha (20% to 53%, p=0.03) had increased, the reduction of the colectomy rate (23.7% to 15%) did not reach statistical significance (p=0.5). Subtotal colectomy was the most common surgery performed (n=40), and surgical complications from all procedures occurred in 33%. In 215/224 (96%) iron deficiency anaemia was detected and in 51% treated, orally (50.2%) or intravenously (49.8%).

Conclusion: Our national audit programme has proven effective to reduce steroid side-effects and iron deficiency anaemia in children with UC. Although over 6 years in the era of biologics there was a trend of decreasing colectomy rates, nearly half of children requiring colectomy had to be operated
non-electively, indicating the importance of early recognition, optimising treatment, and collaborative gastro-surgical assessment. Oral and intravenous iron therapy was efficient and safe. More than half children with rescue therapy received anti-TNFalpha, and nearly 20% of those failed to respond and required colectomy. Subtotal colectomy was required in 13.7% of patients admitted, and complications occurred in one third of surgical patients with UC. Our audit highlights collaborative progress made to implement steroid reduction strategies, prevent iron deficiency anaemia, and to perform elective colectomy in specialised centres.

**Objectives and Study:** Coeliac disease is frequently found amongst first-degree relatives (FDR), illustrating a strong genetic predisposition for the offspring to develop the disease. HLA and genetic variants outside the HLA region explain approximately 54% of the known genetic risk in the general population. Still, the impact of family history on coeliac disease in relation to known risk genes needs to be clarified. The aim was to dissect whether the FDR-type, HLA risk-haplotype and/or distinct single nucleotide polymorphisms contribute to familial predisposition of coeliac disease in a prospective screening study.

**Methods:** Included were 6312 unrelated children with a median age of 9 years (range 1.2-9) carrying either HLA-DQ2 and/or DQ8 who were followed from birth in The Environmental Determinants of Diabetes in the Young (TEDDY) study. Children were screened annually for tissue-transglutaminase autoantibodies (tTGA) from age two years. Coeliac disease diagnosis was based on duodenal biopsies with Marsh score ≥2 or very high tTGA levels. At the time of analysis, 435 were diagnosed with coeliac disease and 72 (16.6%) of them reported a FDR with coeliac disease. Among those 72 with FDRs, 25 (34.7%) reported a mother, 9 (12.5%) a father, 31 (43.1%) a sibling and 7 (9.7%) multiple family members with coeliac disease. The Fisher’s exact test was used for proportion comparisons and hazard ratio (HR) was estimated using Cox proportional hazard model adjusted for gender, HLA and country of residence. Association between coeliac disease and HLA and non-HLA genes in children having a FDR with coeliac disease or not were assessed by logistic regression.

**Results:** Having a FDR with coeliac disease increased the overall risk of developing coeliac disease 4-fold, of which the FDR type affected the disease risk marginally (Table 1). The risk conferred by any FDR varied between HLA haplotypes, being the lowest amongst HLA-DQ2 homozygous children and the highest amongst DQ2 heterozygous children (Table 1). Having a father with coeliac disease was associated with 6-fold risk amongst DQ2 homozygous children, while in DQ2 heterozygous and DQ2 negative children the highest risk was when the mother or multiple family members were affected (Table 1). Four SNPs at PLEK, BAZ2B, ZNF804A and GRB10 loci were associated with familial coeliac disease in children (p< 0.05).
<table>
<thead>
<tr>
<th>операция</th>
<th>матери</th>
<th>отец</th>
<th>брат</th>
<th>другие</th>
<th>HLA homozygotes**</th>
<th>HLA heterozygotes**</th>
<th>HLA negative**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Опасность (95% доверительный интервал), p-значение</td>
<td>общая</td>
<td>HLA homozygotes**</td>
<td>HLA heterozygotes**</td>
<td>HLA negative**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mother</strong></td>
<td>4.2 (2.8, 6.3), &lt;0.0001</td>
<td>3.3 (1.9, 5.8), &lt;0.0001</td>
<td>5.4 (2.7, 10.7), &lt;0.0001</td>
<td>7.9 (2.5, 25.4), 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Father</strong></td>
<td>4.7 (2.4, 9.1), &lt;0.0001</td>
<td>6.0 (2.7, 13.6), &lt;0.0001</td>
<td>3.8 (1.2, 12.1), 0.022</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sibling</strong></td>
<td>3.6 (2.5, 5.2), &lt;0.0001</td>
<td>3.0 (1.9, 4.9), &lt;0.0001</td>
<td>5.1 (2.8, 9.3), &lt;0.0001</td>
<td>3.3 (0.8, 13.7), 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple FDRs</strong></td>
<td>4.4 (1.8, 10.6), 0.001</td>
<td>2.1 (0.5, 8.5), 0.31</td>
<td>10.3 (2.5, 42.4), 0.001</td>
<td>24.2 (3.2, 184), 0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison to coeliac patients without coeliac disease FDR; * Cox regression model adjusted for country, gender and HLA; ** Cox regression model adjusted for country and gender, stratified by HLA

**Table 1. Hazard ratios for type of FDR**

**Conclusions:** Having a FDR with coeliac disease contributes to a lesser effect on the risk of coeliac disease amongst DQ2 homozygous compared with DQ2 heterozygous or DQ2 negative children. This implies that non-HLA risk genes or other familial risk factors play a more important role if carrying the lower risk HLA-haplotypes. There seems to be no familial clustering of non-HLA variants previously associated with celiac disease, indicating other factors affecting the risk of familial coeliac disease.
Prevalence of type-1 diabetes autoimmunity in children at genetic risk for coeliac disease

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Objectives and Study: Coeliac disease (CD) is known to be associated with an increased risk for type 1 diabetes (T1D). We aimed to assess prospectively the prevalence of T1D autoimmunity and manifest T1D in children at increased risk for CD participating in the European multicentre study PreventCD (EU-PreventCD project www.preventcd.com).

Methods: From 2007 to 2010, 944 newborns with at least one 1st degree relative with CD and HLA DQ2 and/or DQ8 positivity participated in a double-blind intervention in which they were randomized to either low amounts of gluten or placebo from end of 4 to 6 months of age. Follow-up visits were scheduled at 4, 6, 9, 12, 18, 24 and 36 months and at least every two years thereafter, which involved measurement of anti-tissue-transglutaminase antibodies. Small bowel biopsies were performed if CD was suspected. At the age of 3 years, serum samples were analysed for T1D-specific islet auto-antibodies against insulin (IAA), GAD (GADA), insulinoma-associated antigen-2 (IA-2A), and two variants of the zinc transporter 8 (ZnT8A, with arginine and tryptophan). If single or multiple islet auto-antibodies were positive, prospective follow-up analyses were performed. If T1D was diagnosed during follow-up but islet autoantibodies were negative at 3 years, serum samples from the PreventCD biobank were analysed retrospectively. Persistent autoimmunity was defined as being positive for islet autoantibodies in 2 consecutive samples. The development of manifest T1D until 1st Dec 2017 was also reported by the study centres.

Results: Samples for analysis of islet autoimmunity at 3 years were available in 706 children, of which 639 (90.5%) were negative, 60 (8.5%) showed single islet autoimmunity, and 7 (1.0%) multiple islet autoimmunity (see table). Among 41 children with single islet auto-antibody positivity and available follow-up samples, 27 turned negative, in 13 single islet auto-antibodies were confirmed, and in one child multiple islet auto-antibodies were found. In 7 patients with multiple islet autoimmunity at 3yrs, follow up samples were available in 5 and confirmed persistent autoimmunity. Thus, a total of 19 children (2.8%, N=685) showed persistent either single or multiple islet autoimmunity. Of the 7 children with multiple islet autoimmunity at age 3 years, two developed CD and two CD and T1D. One child with negative results for islet auto-antibodies at 3 years was diagnosed with T1D at 8.5yrs showing multiple auto-antibody positivity from 5 years onwards.

Conclusion: The prevalence of T1D autoimmunity in this cohort at increased risk for CD was high at 3 years of age. Auto-antibodies were only transiently positive in the majority of those with single auto-
antibody positivity. Only three children from the PreventCD cohort developed manifest T1D until 12/2017. The proportion of CD diagnoses among children with multiple islet auto-antibodies was surprisingly high (4/7, 57%).

### Islet auto-antibodies at 3 years of age

<table>
<thead>
<tr>
<th>Characteristics based on data available until 12/2017</th>
<th>All negative N=639 (90.5%)</th>
<th>Single positivity N=60 (8.5%)</th>
<th>Multiple positivity N=7 (1.0%)</th>
<th>ALL (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last follow-up [yrs ± SD]</td>
<td>8.9 ± 1.4</td>
<td>9.2 ± 1.2</td>
<td>8.2 ± 3.3</td>
<td>8.9 ± 1.4</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>298 (47%)</td>
<td>29 (48%)</td>
<td>3 (43%)</td>
<td>330 (47%)</td>
</tr>
<tr>
<td>Received gluten from 4 months of age n (%)</td>
<td>316 (50%)</td>
<td>32 (53%)</td>
<td>5 (71%)</td>
<td>353 (50%)</td>
</tr>
<tr>
<td>Persistent islet auto-antibody positivity in follow-up sample (if available) n (%)</td>
<td>---</td>
<td>14 / 41 (34%)</td>
<td>5 / 5 a (100%)</td>
<td>19 / 685 a (2.8%)</td>
</tr>
<tr>
<td>Diagnosis of T1D during follow-up n (%)</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>2 (28.6%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Diagnosis of CD during follow-up n (%)</td>
<td>83 (13%)</td>
<td>8 (13%)</td>
<td>4 c (57%)</td>
<td>95 (13%)</td>
</tr>
</tbody>
</table>

* One child was diagnosed with manifest T1D at 3yrs which was considered as persistent autoimmunity.

Follow-up samples were not available in 19 children with single and 2 children with multiple islet autoimmunity which were therefore excluded for calculation of the prevalence of persistent islet autoimmunity

Includes the 2 children which also developed T1D; one child was diagnosed at 3 years followed by CD diagnosis at 4.5 years, the other child was diagnosed both for T1D and CD at 5.5 years. The two children with CD only were diagnosed with 3.3 and 4 years.

Table: Characteristics of children stratified by T1D islet autoimmunity at 3 years

**Disclosure of interest:** The present analyses were funded by a grant of the Nutricia Research Foundation, project 2010-37.
Exploring the gut-thyroid axis in paediatric coeliac disease patients of Hellenic origin reveals selected genomic variants in CTLA4, BACH2, and IL23R genes that may account for overlapping susceptibility between Graves' disease and paediatric coeliac disease

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Objectives and Study: The molecular determinants and cross-talk in cell signaling of the gut-thyroid axis are still unravelled rendering differential diagnosis and theranostics of a series of autoimmune inflammatory disorders. Several genetic, epidemiological, clinical, serological, and pathophysiological data indicate that coeliac disease is associated with autoimmune thyroid disorders and in particular, Graves' disease. Notwithstanding, no clear nomogram is effective today to allow for optimum disease management and patient stratification. Herein, we explore the role of single nucleotide polymorphisms in selected genes for overlapping susceptibility between Graves' disease and paediatric coeliac disease aiming for an immunogenetic model towards the identification of coeliac disease patients with an increased risk of developing Graves' disease.

Method: Extensive data mining, pathway analysis and literature review resulted in the selection of genomic variants in CTLA4, BACH2 and IL23R genes. For data validation, coeliac paediatric patients of Hellenic origin (n=109) and their ethnically matched counterparts (n=111) were genotyped by PCR and Sanger sequencing. Hardy-Weinberg equilibrium was determined by Pearson’s goodness-of-fit chi-square, log-likelihood ratio chi-square and Exact tests. Genotype and allele frequencies were evaluated by the Fisher’s Exact test. A two-tailed p-value of &LT; 0.05 was considered statistically significant. The R project for statistical computing (R i386 3.2.1) was used.

Results: Selected genomic variants in CTLA4, BACH2 and IL23R genes may account for the overlapping susceptibility between Graves' disease and paediatric coeliac disease in patients of Hellenic origin

Conclusion: Genomic variants in CTLA4, BACH2 and IL23R genes may serve as the building block of a nomogram to optimize Graves' and Coeliac disease management and patient stratification.

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Systemic antibiotics in the first year of life is associated with an increased risk of diagnosed coeliac disease

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Objectives and Study: The objective of this study was to investigate the association between dispensed prescriptions for systemic antibiotics in the first year of life and diagnosed coeliac disease in two large independent population cohorts from Scandinavian countries with different prevalences of diagnosed coeliac disease.

Method: We used data from administrative registers and health administrative registers in Denmark and Norway. The outcome was diagnosed coeliac disease. The main exposure was a dispensed prescription for a systemic antibiotic in the first year of life (yes/no). In sub-analyses we examined the number of antibiotic courses, the type of antibiotics (penicillin, extended spectrum penicillins, macrolides and other systemic antibiotics), the age at antibiotic dispense (3 months intervals) and the age at first antibiotic dispense (3 months intervals). Data were analysed by logistic regression and adjusted for year of birth because of different follow-up times. Furthermore, we adjusted for the potential confounders: sex, season of birth, maternal parity, maternal education and maternal age, gestational age and weight for gestational age. As a sensitivity analysis we adjusted for a hospital admission for an infectious disease in the Danish cohort.

Results: For the analysis of the Danish cohort we included 1 168 656 children born from 1 January 1995 to 31 December 2012. Coeliac disease was diagnosed in 1427 children (0.12%). A systemic antibiotic was dispensed to 451 196 children without coeliac disease (38.7%) and 622 children with coeliac disease (43.6%).

For the analysis of the Norwegian cohort we included 541 036 children born from 1 January 1995 to 31 December 2012. Coeliac disease was diagnosed in 1920 children (0.35%). A systemic antibiotic was dispensed to 98 821 children without coeliac disease (18.3%) and 391 children with coeliac disease (20.4%).

A dispensed prescription for a systemic antibiotic in the first year of life was associated with diagnosed coeliac disease in both cohorts (Norway: adjusted odds ratio (aOR): 1.26. 95% confidence interval (95% CI): 1.12-1.41. Denmark: aOR 1.27. 95% CI: 1.14-1.42). We found a dose-response relationship between an increasing number of dispensed prescriptions and coeliac disease (Norway: aOR: 1.06. 95% CI: 1.05-1.08. Denmark: aOR: 1.05. 95% CI: 1.03-1.07). Adjustment for hospital admissions for an infectious disease did not change the conclusions.

We found no statistically significant difference between groups for the age at antibiotic dispense or for the age at first antibiotic dispense. The association did not differ significantly between types of antibiotics (penicillin, extended spectrum penicillins, macrolides, and other systemic antibiotics).

Conclusion: In this large observational register-based study of two population cohorts, dispensed prescriptions for systemic antibiotics in the first year of life was associated with an increased risk of diagnosed coeliac disease.

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The large majority of coeliac children, adolescents and adults have a high degree of perceived dietary competence

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Objectives and Study: Currently the only treatment for coeliac disease (CD) is a lifelong gluten-free diet (GFD). A GFD involves dietary restrictions which may impact a person's Health-Related Quality of Life (HRQoL).

Studies have pointed to the importance of the person's perception of competence in managing and complying with a GFD. Perceived competence has been assessed in various clinical settings. The aim of the present study was to develop the Perceived Competence Scale for adhering to a GFD (PCSGFD): a short and precise CD-specific patient-reported outcome measure for children, adolescents and adults.

Methods: The PCSGFD was developed in three phases: In phase 1 the scale was developed in line with the scales 'Perceived Competence (Maintaining a Healthy Diet)' and 'Perceived Competence for Diabetes' (2). The four PCSGFD-items were: 1) I am confident in my ability to adhere to a gluten-free diet. 2) I am able to adhere to a gluten-free diet now. 3) I am able to adhere to a gluten-free diet in the future. 4) I am able to meet the challenges of adhering to a gluten-free diet. The answer scale was: 1 not at all true, 2, 3, 4 somewhat true, 5, 6, and 7 very true. The PCSGFD score is the arithmetic mean of the four items. Please note that the items are translated directly from Danish.

In phase 2 the PCSGFD was presented to members of the target population (n=24) in cognitive interviews aimed at assessing the reception and understanding of the PCSGFD.

In phase 3 the PCSGFD was programmed into a web-based questionnaire and distributed to the target population through the national patient organization, CD-specific social media groups and hospital outpatient clinics. The PCSGFD was distributed alongside questionnaires on background variables, self-reported CD-symptoms, generic quality of life (WHO-5) and CD-specific HRQoL (CDQL).

Results: A total of 896 respondents completed the PCSGFD. The 816 respondents who indicated they were diagnosed with CD were retained in the analysis. The average age of the CD respondents was 37.61 years (SD=16.48), with an expected surplus of females (89%).

We found that males (M = 5.90, SD = 1.61) tended to score lower than females (M = 6.16, SD = 1.37) on the PCSGFD (p = .114).

Respondents younger than 18 years (N = 94) scored significantly lower (M = 5.78, SD = 1.48) than adults (M = 6.18, SD =1.38) on the PCSGFD (p = .01).

The psychometric properties of the PCSGFDS were assessed showing excellent internal reliability (α= 0.96) and satisfying construct validity with positive correlations with WHO-5 (p &LT; .001) and CDQL (p &LT; .001) and negative correlation with the reported number of dietary transgressions (p&LT; .001).

Conclusion: The PCSGFD is psychometrically robust and measures patient-perceived competence in following a GFD. We found that a low score on the PCSGFD correlated with the reported number of dietary transgressions. Furthermore, PCSGFD correlated well with the HRQoL-measures. Thus the scale may act as an easy and useful tool in assessing patient HRQoL and difficulties in complying with the only available treatment for CD; the GFD.

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GASTROENTEROLOGY - Inflammatory bowel disease

G-O-042

Long-term outcomes of pediatric patients admitted with acute severe colitis - a multi-center study from the pediatric IBD Porto group of ESPGHAN

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Objective: Nearly 30% of pediatric ulcerative colitis (UC) patients develop acute severe colitis (ASC) flares requiring admission. Colectomy rates in these cases vary in different studies, ranging between 10-30%. However, most of these studies have been conducted in the pre-biologic era, and have provided follow-up only up to a year after admission. Our objective was to define the long-term outcomes of pediatric UC patients admitted with ASC.

Methods: This was a multicenter retrospective study from centers affiliated with the Pediatric IBD Porto Group of ESPGHAN. Data on pediatric UC patients admitted during 2009-2011 for ASC flares was collected at 4 different time-points: admission and 1, 3 and 5 years following admission. The primary outcome was to define colectomy rates at each time point.

Results: A total of 96 UC patients that were followed for 5 years after an ASC admission were included in this study. The mean age of the patients at diagnosis of UC was 12.3 years; 79% of them presented with extensive disease or pan-colitis. The mean age at ASC admission was 13.2 years. Twenty four percent of the patients were considered steroid non-responders, and 8 patients (8.3%) underwent colectomy during the initial admission. Overall, colectomy rates at 1, 3 and 5 years post-ASC admission were 27%, 32% and 34%, respectively. Interestingly, steroid-responsiveness during initial ASC admission did not predict colectomy-free survival rates at 1, 3 and 5 years.

Conclusions: High colectomy rates were reported in our cohort, mainly in the first year following ASC admission. Additional long-term prospective studies are required to determine whether therapeutic drug monitoring and increased infliximab dosing during ASC flares reduce surgery rates in these patients.

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Looking the truth in the eye - benchmarking care and outcomes against the world's largest paediatric IBD registry

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Objectives and Study: Medical management of children with inflammatory bowel disease (IBD) is challenging, complex and informed by numerous guidelines. Despite the well-described benefits of benchmarking clinical practice, the vast majority of paediatric IBD centres in the UK do not measure clinical outcomes. ImproveCareNow (ICN) is a US health-learning network that includes data on over 25,000 children. It includes monthly webinars to share learning and innovation, offers access to an extensive online ‘exchange’ of ideas, and supports improvement initiatives to improve individual care and population outcomes. Membership also provides units with monthly data on their patient population, benchmarked against over 100 other paediatric IBD centres. The aim of this study is to assess outcomes of care and identify areas for improvement in children with IBD managed at Addenbrookes Hospital, Cambridge.

Method: We report IBD related outcome data of 164 children currently active within the ICN2 Registry (> 75% of all children eligible for enrolment in Cambridge). 54% have Crohn’s disease (CD), 31% ulcerative colitis (UC) and 15% with IBD-unclassified (IBD-U). Data is presented as % of eligible patients, compared to the average of all participating centres with ≥75% of patients enrolled, versus the network’s defined targets (control numbers given in brackets). We await data from ICN network on the correlation between % remission rates and biologic use.

Results: Currently, 70% (ICN control group 81%; declared network target 83%) of all eligible paediatric IBD patients are in clinical remission. 94% (96%; 95%) are currently not taking prednisone. 74% of our patients with CD (and 82% in the control group) are in clinical remission. 69% (78%) of the UC patients are in clinical remission. 85% (90%; 90%) of all children with IBD feature a satisfactory nutritional status and 98% (93%) show a satisfactory growth status. TPMT activity was measured in 100% (83%; 90%) of all IBD patients when treatment with thiopurine was started and thiopurine dose was administered according to ICN model care guidelines in 97% (64%; 80%) of patients.

Conclusion: Children with IBD managed in Cambridge appear to fall below US peer group and network targets for clinical remission. Having identified such gaps, work is now underway to understand the drivers for this disparity. We will clarify whether or not the major driver for an improved remission rate in the best US centres is due to earlier / more frequent use of biologic medication. Without accurate, population-based measures, improvements in clinical outcome cannot be documented. Embedding quality improvement and benchmarking of clinical outcomes in children with IBD allows i) identification of areas for improvement, and ii) impact of any change in management. Such large health-learning networks provide substantial advantages over standard audit / registry data. Assessment of the key drivers for differences in clinical outcomes between US and European PIBD units, may lead to beneficial changes in practice.
Predicting relapse in new-onset Crohn disease - results of the prospective GROWTH CD Study

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Objectives and Study: Children with Crohn’s disease (CD) are at a high risk for complications from both disease and treatment. The early stratification of patients by risk could avoid under- or over-treatment, while reducing potential adverse outcomes from treatments or disease. The goal of the present study was to develop predictive models for high or low risk disease relapse from factors identified within the first 12 weeks from diagnosis.

Method: The GROWTH CD study (Growth, Relapses and Outcomes With THerapy) was a prospective study designed to identify early factors that could predict subsequent outcomes such as disease relapse during follow up. Newly diagnosed children underwent colonoscopy, gastroscopy and imaging. They were phenotyped by the Paris classification and followed at baseline, 8, 12, 26, 52, 78 and 104 weeks. Twenty eight dichotomous and continuous variables from baseline and/or week 12 were assessed, including phenotype, inflammatory markers (ESR, CRP, Calprotectin), disease activity (PCDAI and PGA) and serum albumin. Clinical relapses at any time point from week 12-104 were recorded. Logistic regression and risk modelling was performed for best fit models.

Results: Two hundred and eighty two patients with baseline and week 12 data were available. Of these, 178 (64\%) patients had remission induced (PCDAI < 10) by week 12 and were included in the subsequent analysis. Seventy six patients (43\%) had a disease relapse during follow up. Of baseline parameters, only higher PCDAI score was significantly associated with an increased risk for relapse (p<0.03). Following multivariate analysis of week 12 data, elevated CRP (p=0.02), higher PCDAI score (p=0.02) and faecal calprotectin > 400 mcg/g (p=0.03) were significantly associated with subsequent disease relapse. A final prediction model including gender, age, PCDAI score, calprotectin and CRP at week 12 showed a sensitivity of 43\%, specificity 92\%, PPV 78\%, NPV 71\% and correctly predicted 76.8\% of the population that relapsed.

Conclusion: Following induction of remission, higher PCDAI score, CRP and calprotectin >400 mcg/g at week 12 were associated with subsequent disease relapse. Baseline characteristics did not successfully predict relapse in this cohort.

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Investigating CD8+ T-cell gene expression signatures as potential prognostic biomarkers in paediatric inflammatory bowel disease

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Objectives and Study: Inflammatory Bowel Diseases (IBD) are characterized by a relapsing-remitting disease course, with severity varying substantially amongst patients. At present, no reliable prognostic biomarkers are available for clinical practice. Previous work on adult patients identified CD8 positive T-cell gene expression as a promising prognostic biomarker in IBD (Lee JC, et al. JCI 2011). The aim of this study was to investigate CD8+ T-cell gene expression as a prognostic biomarker in children newly diagnosed with IBD.

Method: 112 children (age 5-16) were prospectively recruited at diagnosis and CD8+ T-cells isolated from a peripheral blood sample using magnetic bead sorting. Subsequently, RNA was extracted and genome wide expression profiling performed on Affymetrix Human Gene ST 2.0 Arrays. Detailed clinical phenotype and disease outcome data was recorded for all patients (minimum follow-up: 1.5 years). Bioinformatic analysis was performed using “R” and various Bioconductor packages, and included consensus clustering, differential gene expression analysis (DGEA), survival analysis (Kaplan Meier), and weighted gene co-expression network analysis (WGCNA).

Results: Results are currently available from a discovery cohort of 42 children (22 Crohn's (CD), 20 ulcerative colitis (UC)). Unsupervised consensus clustering identified two main groups indicating distinct differences in global CD8 expression signatures amongst IBD patients. DGEA between these groups revealed 1324 annotatable genes, 20% of which were found to overlap with the prognostic expression signatures previously identified in an adult IBD cohort (P 2.67 e-100 from hypergeometric test). WGCNA performed separately in children with CD (n=22) and UC (n=20) identified modules (groups of genes), some of which correlated strongly (Pearson correlation index >0.6, p< 0.05) with individual outcomes including number of treatment escalations, use of biologics and surgical interventions. Performing unsupervised hierarchical clustering using genes derived from these modules followed by Kaplan Mayer survival analyses revealed highly significant differences in disease outcome between patient groups (Figure).
Conclusion: Our results derived from a subset of available patients support CD8+ T-cell gene expression signatures as promising prognostic biomarkers for children newly diagnosed with IBD. These paediatric signatures partly overlap with the genes identified in adult patients with IBD from previous studies, possibly suggesting distinct differences between adult and paediatric onset IBD.

Disclosure of interest: The main funders for this research project are CICRA (Crohn's in Childhood Research Association), Crohns and Colitis UK, The Broad Foundation. No conflicts of interest to declare.

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A treat-to-target strategy guided by Pan-enteric valuation in paediatric Crohn's disease improves outcomes at 2 years

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Objectives and Study: Sparse data exist on the long-term outcomes of mucosal healing (MH) in children with Crohn's disease (CD). It is uncertain if a treat-to-target approach might be a clinically and cost-effective strategy improving deep remission (DR) rate and outcomes. Previously, we reported MH and DR rates on the entire GI tract by performing three pan-enteric capsule evaluations and applying a treat-to-target strategy over 52 weeks in children with CD. This study evaluates the impact of this approach at 104-weeks.

Methods: Children with known CD were prospectively recruited and underwent pan-enteric capsule endoscopy (PCE) at 0, 24, 52 and 104 weeks. Therapy was calibrated according to PCE and magnetic resonance enterography (MRE) results in a treat-to-target approach. Results at week 52 and 104 were compared, and long-term outcomes between patients with or without complete MH were calculated using an intention-to-treat (ITT) analysis of clinical relapse, need for steroids and/or treatment escalation, hospitalization and surgery.

Results: Forty-eight patients (pts) were recruited at baseline and underwent a treat-to-target approach for one year. The 52-week assessment demonstrated a 58% DR rate compared to 21% of baseline (p< 0.05). In all, 42 underwent the 104-week PCE evaluation (2 developed an ileo-cecal valve stricture at 52 weeks; 4 were lost to follow-up). MH was present in 10 at baseline; 28 at 52 weeks. There was only 7% drop-off in MH compared with 1-year assessment. In ITT analysis, complete MH at 52 weeks was associated with decreased clinical relapse rate (p< 0.003), reduced steroid usage (p< 0.0005), fewer treatment escalation (p< 0.0003), and diminished hospitalization rates (p< 0.0001). There was a decreased need for surgery, but not statistically significant (p=0.065). The overall diagnostic yield of PCE, MRE and biomarkers were 54%, 37% and 33%, respectively.

Conclusion: Treat-to-target approach can significantly increase DR rates on the entire GI tract by using PCE and it seems to be cost-effective. When MH is achieved by this strategy, it is sustainable (93%) over a one-year period and correlates with improved patient outcomes, including decreased need for steroids, treatment escalation, hospitalization and surgery.

Disclosure of interest: Salvatore Oliva and Stanley Cohen are consultants for Medtronic. All other authors have no financial disclosure to declare. No honorarium, grant, or other form of payment was given to anyone to write and to produce the manuscript.

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Incidence and characteristics of rare and severe complications in children with paediatric-onset IBD; the international PIBD SETQuality Safety Registry by PIBDnet

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Objectives and Study: Paediatric-onset inflammatory bowel disease (PIBD) reflects a more severe disease compared to adult forms, which leads to more intensive therapy strategies earlier in the disease course. This exposes children to a risk of serious disease- and treatment related adverse events. Currently, numbers on the occurrence of those rare events as well as specifics on disease course and therapy are lacking. It is essential to characterize patients at risk in order to prevent severe outcomes. This study aims to identify risk factors for severe outcomes in PIBD and determine their incidence rates.

Method: An electronic safety registry was designed to prospectively identify PIBD patients < 19 years of age that develop a severe IBD- or IBD treatment related complication. Paediatric gastroenterologists in 23 countries are requested to register every month whether they observed one of the 10 listed complications. This list, designed with input from the PIBD SETQuality consortium, includes; cancer, death, severe neurological disease, renal failure, venous thromboembolism, liver failure, sepsis, opportunistic infections, bone marrow failure and hemophagocytic lymphohistiocytosis (HLH). In addition, other rare and severe complications outside the listed categories are also requested and checked for eligibility. For every registered complication detailed anonymized information on patient- and disease characteristics, therapy and the specific complication is obtained. Concurrently, reporting doctors complete an annual survey that collects data regarding the number of new and current PIBD cases within their practice, and their regional coverage. To analyse the data the Nomenclature of Territorial Units for Statistics (NUTS3), which includes validated population numbers defined by Eurostat1, is used to calculate incidence numbers per country and region based on the Poisson distribution for rare events.

Results: Since October 2016 we have received 793 responses from 20 European and 3 other countries. In total, 125 doctors are actively participating in this safety registry. Since the start of this project, monthly response rate has increased from 42% in the first month to 61% in the last month. In total 74 complications were reported of which 41 were followed up after checking eligibility and removal of duplicates. Sepsis (n=6) and opportunistic infections (n=5) were most frequently reported, followed by bone marrow failure (n=4), renal failure (n=4), venous thromboembolism (n=4), cancer (n=3) and neurological disease (n=3). The remaining reported cases were death (n=2) and liver failure (n=2). No cases of HLH were registered. Eight complications were reported as other, but none of those comprised the same type of complication. Incidence rates of reported complications are shown in Table 1.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of reported complications</th>
<th>Incidence per 1000 PIBD patients</th>
<th>95% Poisson CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>22</td>
<td>7.4</td>
<td>4.7-11.0</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>7</td>
<td>6.7</td>
<td>3.0-13.3</td>
</tr>
<tr>
<td>Italy</td>
<td>3</td>
<td>4.1</td>
<td>1.1-11.3</td>
</tr>
<tr>
<td>Germany</td>
<td>1</td>
<td>6.7</td>
<td>0.3-33.0</td>
</tr>
<tr>
<td>Israel</td>
<td>3</td>
<td>5.7</td>
<td>1.4-15.4</td>
</tr>
<tr>
<td>Average (weighted)</td>
<td>-</td>
<td>6.9</td>
<td>4.9-9.4</td>
</tr>
</tbody>
</table>
[Table 1.]

**Conclusion:** Over a one-year period 41 rare and severe complications in PIBD patients were prospectively identified. Incidence rates of reported complications seem to be comparable amongst different countries and show that those complications are indeed rare. Follow up forms with additional information on every reported complication are being collected to allow further analysis and understanding of the possible causes, management and outcomes.


**Disclosure of interest:** This study is part of a study funded by Horizon 2020. Funding source number: 668023 PIBD-SETQuality

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Sensitisation to common food allergens and aeroallergens in relation to functional gastrointestinal disorders in adolescents: results from the GINIplus and LISA birth cohorts

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Objectives and Study: The cause of functional gastrointestinal disorders (FGIDs) is unclear, but the frequently observed overlap of FGIDs and atopic diseases suggests a possibly shared pathophysiology involving immune dysregulation. Very few studies have assessed the role of allergen sensitisation in relation to FGIDs. This study assessed the prospective and cross-sectional relationship between sensitisation to common food allergens and aeroallergens measured at various time-points, and FGIDs at age 15 years.

Method: Children participating in the GINIplus and LISA birth cohort studies with data on FGIDs, allergic sensitisation at ages 1, 2, 3, 6, 10 and 15 years (at times limited to subgroups), and predefined confounders, were included (N=3521). Allergic sensitisation was defined as specific IgE serum levels ≥0.35 kU/L, to food allergens or aeroallergens, respectively. Self-reported symptoms of FGIDs were assessed at age 15 years by a validated age-appropriate questionnaire created as part of the Rome III process. Using adjusted logistic regression, cross-sectional and prospective associations of allergen sensitisation with FGIDs (total FGIDs, and specifically, functional abdominal pain disorders, including abdominal migraine and irritable bowel syndrome) were assessed.

Results: The prevalence of FGIDs in the total study population was around 13%. Functional abdominal pain disorders were the most prevalent, affecting 11% of the study population. Cross-sectionally, no association was observed for sensitisation against food or aeroallergens with FGIDs at age 15 years. Aeroallergen sensitisation at age 10 years was inversely associated with FGIDs at age 15 years (OR=0.75 [95%CI=0.57;0.99]). In a subgroup of children from the GINI cohort with a positive family history of allergic disease, assessed at ages 1 and 3 years, food allergen sensitisation at age 1 year was significantly associated with abdominal migraine at age 15 years (2.55 [95%CI=1.11;5.83]), and at age 3 years with total functional abdominal pain disorders (2.25 [1.24;4.09]). These associations were not replicated in sensitivity analyses limiting the samples at ages 2, 6, 10 and 15 years to children with a positive family history of allergic disease.

Conclusion: Results from the present analyses do not support the hypothesis that sensitisation to food or aeroallergens are associated with or are a marker for FGIDs in adolescence. In a subset of children from the GINI cohort with family history of allergic disease, sensitisation to food allergens early in life was associated with an increased risk of later functional abdominal pain disorders. Due to the distinct characteristics of this subgroup of the study population, residual confounding cannot be ruled out. Further studies are hence required to confirm these findings.

Disclosure of interest: This work was partly finantially supported by Mead Johnson. The funding body had no influence on the work carried out.

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Long-term treatment with proton-pump inhibitors is effective in children with eosinophilic esophagitis

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Objectives: Proton pump inhibitor responsive oesophageal eosinophilia (PPI-REE) is frequently observed in children, in our own experience 66% of children with oesophageal eosinophilia responded to PPI. Evolving evidence has emerged that PPI-REE has similar characteristics than eosinophilic esophagitis (EoE), as stated in the recent European evidence-base guidelines, and PPI should be considered as another treatment (Lucendo A, et al. United Eur Gastroenterol J, 2017). Chronicity is a main characteristic of EoE, so maintenance treatment is important. Prospective studies of clinical and histological recurrence while on PPI maintenance therapy have not been addressed in children to date. The objective of this study is to evaluate the long-term efficacy and safety of PPI therapy in children with EoE.

Methods: This prospective study enrolled consecutive children with EoE diagnosed according to the recently published European guidelines that presented histological response to 8 weeks esomeprazole trial (1mg/kg/dose twice daily) (Gutiérrez-Junquera C et al., JPGN, 2016). Esomeprazole was continued at a maintenance dose of 1mg/kg/day dose for one year. Symptoms recurrence was monitored and follow up endoscopy was performed at 12 months or longer on PPI maintenance dose or before if symptoms reappeared. Histological relapse was defined as presence of ≥15 eos/hpf, complete response as <5 eos/hpf and partial response as ≥5 and <15 eos/hpf in oesophageal biopsies. No patient had dietary restrictions or topical steroid therapy.

Results: One hundred nine children received 8 weeks PPI initial treatment with esomeprazole, and 72 (66%) showed histological response. Sixty patients received maintenance treatment and completed one year follow up. Two patients were lost in follow-up and in one patient parent refused another endoscopy. Finally, 57 children (73.7% male, median age 11 years) were enrolled in the study. Follow-up endoscopy was performed at a median time of 14.5 months. Ongoing histological response was present in 40 (70.1%; 95% CI: 56.5; 81.5) children, complete response in 32 and partial response in 8 patients. Only 17 children (29.9%) displayed histological recurrence at follow-up. Forty-nine (86%) children remained asymptomatic, 3 (5.3%) had mild symptoms and in 5 (8.8%) patients symptoms persisted unchanged. Pre-treatment clinical and endoscopic scores, median peak eosinophil count and median PPI dose/kg/day were similar in relapsers and non-relapsers. In relation to initial histological response after 8 weeks PPI trial, 81% (30/37) of children with complete response showed long-term histological response; compared to only 50% (10/20) of those with partial histological response (p=0.014). Mild adverse effects were observed only in 5 children (diarrhoea, headache, abdominal pain and rash). Twelve children have received esomeprazole at 0.5 mg/kg/day with follow-up endoscopy after 12 months (2 years follow-up) and ongoing histological response was present in 11 (91.6%) of them.

Conclusion: Most PPI-responsive EoE children remain in histological and clinical remission on lower dose maintenance treatment at one-year follow-up with an adequate safety profile. Complete histological response to 8 week PPI trial was associated with higher probability of ongoing histological response.
Frequency of long-term histological response in relation to initial histological response

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A partly fermented infant milk formula with scGOS/lcFOS reduces stress-induced gut permeability and gut hypersensitivity in rats

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Objectives: An intact gut epithelial barrier is key in maintaining intestinal immune homeostasis and can be modulated by the gut microbiota. Environmental factors like stress and antibiotics negatively impact the gut barrier/permeability, which results into a proinflammatory immune response and can also lead to visceral hypersensitivity. An infant milk formula (IMF) combining a specific fermented milk powder (unique fermentation process fermented by Streptococcus thermophilus 065 (ST065) and Bifidobacterium breve C50 (BbC50); Lactofidus™) and prebiotic scGOS/lcFOS (0.8 g/100 ml, 9:1) has previously been reported to improve gut comfort in infants with minor digestive problems. In healthy term infants, this partly fermented IMF with scGOS/lcFOS showed a lower incidence of infantile colic. Moreover, in colicky infants a disturbed gut motility linked to a hyperalgesic colonic hyperperistalsis (painful gut contractions) has been described. Up to now mechanistic insight in how this partly fermented IMF with scGOS/lcFOS impacts gut homeostasis is lacking. In this context, we investigated the impact of the partly fermented IMF with scGOS/lcFOS) (fermented IMF) versus non-fermented IMF with and without prebiotic on visceral sensitivity and the effect of fermented IMF on gut permeability in a rat physical restraint stress model, which is known to display increased gut permeability and visceral hypersensitivity.

Method: Wistar rats were daily administered with the fermented IMF, non-fermented IMF with and without prebiotic (1 ml/rat) or NaCl (0.9%, 1 mL/rat) for a period of 14 days. At day 14, abdominal contractions, (i.e. electromyography response) upon colorectal distension were measured in both basal condition and 30 minutes after partial restraint stress (PRS) as parameter for visceral sensitivity. In addition, gut paracellular permeability was evaluated using ⁵¹Cr-EDTA administered orally to the fermented IMF group that was either submitted to PRS or not.

Results: Under basal condition treatment with fermented IMF or non-fermented IMFs did not modify visceral sensitivity in response to CRD compared to control (NaCl). After PRS, the number of abdominal contractions at 0.8 and 1.2 mL in response to CRD significantly increased in control illustrating visceral hypersensitivity. Fermented IMF showed an inhibitory effect on PRS-induced visceral hypersensitivity, whereas the non-fermented IMFs did not show this effect. Moreover, fermented IMF also limited the PRS-induced intestinal hyperpermeability.

Conclusion: This study shows that fermented IMF has anti-hyperalgesic effects and limits the increase in gut permeability that is associated with PRS in rats. Taken together, these data suggest that the partly fermented IMF with scGOS/lcFOS (9:1) reduces gut hypersensitivity by normalizing the intestinal epithelial barrier possibly via a synergetic interplay between the ST065 and BbC50 strains and/or fermentation (by)products (also referred to as postbiotics) in the IMF. Future research should give more insights into the link between gut epithelial barrier, mucosal immune response, gut sensitivity, and the impact of the fermented formula thereon.

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Predictive factors of histological complication in EA-TEF patients during 10 years’ prospective endoscopic follow-up

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Objective and Study: Endoscopic follow up after oesophageal atresia (OA) repair is indicated to detect histological complications, mostly due to the high prevalence of gastro-oesophageal reflux in this population. It is also recommended to systematically treat these patients with antacid medications after surgical repair. Our aim is to study the prevalence of histological esophageal complications (peptic oesophagitis, gastric metaplasia and eosinophilic oesophagitis) and to determine predictive factors for these complications in a cohort of OA patients followed up to 11 years.

Patients and methods: This is a prospective longitudinal cohort study of 77 children with OA, born from September 2005 to December 2014. Outcome was evaluated at study end in February 2017.

Results: Among the 77 patients, (44 males) included, 66 patients (85%) had type C OA, 8 (10%) had type A, 3 had type D. A long gap OA was present in 16 patients (22%) with the same proportion of type A and C. All patients had a proton pump inhibitor (PPI) (n=73) or an H2 receptor antagonist (n=4) treatment started before the first month of age. 252 endoscopies were performed in 73 patients (mean 3.4 per patient, range 1 to 29). Histological complications were diagnosed in 35 patients (45%) at a median age of 4.9 years. Peptic oesophagitis was demonstrated in 32 and was significantly associated with an history of anastomotic leak (Odds Ratio (OR) 7.2 [95%CI 2.07-25]; p<0.001) and with recurrent anastomotic stricture (OR 4.3 [95%CI 1.33-14.0]; p=0.01). Gastric metaplasia was present in 9 patients, and was associated with recurrent stricture (>3 dilations) (OR 5.4 [95%CI 1.26-23.2]; p=0.01). Eosinophilic oesophagitis was seen in 15 patients and significantly associated with presence of peptic esophagitis (OR 4.8 [95%CI 1.37-17.1]; p=0.01) and gastric metaplasia (OR 12.2 [95%CI 2.6-57]; p=0.003). After multivariate analysis, anastomotic leak was significantly associated with a higher risk to develop peptic esophagitis (p= 0.0008, HR 3.18 [95%CI 1.56-6.49]) and anastomotic recurrent strictures (> 3 dilations) was associated with the occurrence of any histological complications (HR 3.11 [95%CI 1.53-6.34]). There was no association between the result of the first endoscopy and the occurrence of histological complications during follow-up (p-value=1.0, OR 0.8 [95%CI 0.16, 3.96].

Conclusion: Histological complications with potential long-term consequences are found in nearly 50% of the patients with OA treated with PPI or H2RA after surgical repair. An history of anastomotic leak and/or recurrent anastomotic strictures is associated with the occurrence of these complications. The result of the first endoscopy does not predict the occurrence of histological complications during follow-up. This highlights the importance of a close and systematic long-term follow-up of these vulnerable patients in specialized multidisciplinary clinics including endoscopy and biopsies.

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Automated detection of infant crying and fussing for clinical applications

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Objectives and Study: Excessive crying and fussing of unknown cause in infants is common and of relevant parental concern, and diagnoses traditionally derive from subjective parental reports. To date, no method for the automated detection and quantification of crying and fussing exists to provide an objective metric for diagnostic and clinical study purposes. The aim of the research reported here was to utilize the LENA (Language ENvironment Analysis) system to automatically identify, quantify, and distinguish periods of crying versus fussing in a pilot sample of infants. Model performance is presented comparing simultaneously generated parental report diaries, and clinical applications of the technology are discussed.

Method: The LENA system comprises a small digital audio recording device fitted in specialized clothing worn by the child plus processing software. The device enables the continuous capture of up to 24 hours of each child's natural sound environment, and the software automatically processes the recorded audio data to generate metadata on distinct sound categories, including child cries. As a first step, a new algorithm was generated by machine learning, and then validated in a human-rated sample of 124 cry periods from 41 infants. An observational pilot study of 12 term infants is currently ongoing where parents record crying and fussing with diaries in parallel to LENA recordings in order to enable a direct comparison of both.

Results: The new algorithm distinguished periods of crying from fussing with 90% sensitivity, 92% specificity, and 91% overall accuracy in the validation sample. Relevant differences between parental diary reports and automatically detected absolute crying and fussing duration, time resolution, and distribution have been observed in the ongoing pilot study.

Conclusion: Machine-based learning algorithms were developed to reliably and objectively identify and distinguish crying from fussing and to quantify both in recordings obtained using the LENA system. Ease of use, objectivity, and high temporal resolution are relevant advantages of this innovation as compared to parental diaries. Differences between automated detection and parental report diaries were detailed, and results from this ongoing research were reported to validate the utility of the automated method in the current and other potential clinical applications, such as identifying and characterizing infantile colic.

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Therapeutic efficacy of ginger on vomiting in children with acute gastroenteritis

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Objectives and Study: Vomiting is reported in up to 75% of children with acute gastroenteritis (AGE), contributing to fluid loss, oral rehydration failure and hospital admissions. Approximately 80% of Italian family pediatricians (FPs) commonly use antiemetic drugs in children with AGE, and the most available antiemetic agents are often used off-label in children. Evidence support the therapeutic efficacy of Zingiber’s officinalis rhizome, better known as ginger, in pregnancy or chemotherapy-associated vomiting in adult patients.

We aimed to evaluate the potential therapeutic efficacy of ginger on vomiting in children with AGE.

Main study outcome was the rate of children presenting vomiting after the first treatment dose. Secondary outcomes were the daily number of vomiting episodes, school days lost by the children, hospitalization, and diarrhea duration. The possible occurrence of adverse events was also assessed.

Method: Randomized, double-blind, placebo-controlled trial performed in collaboration with FPs operating in the city area of Naples, Italy. Otherwise healthy children aged 1-10 years, with recent occurrence of signs and symptoms of suspected AGE with appearance of vomiting (no bilious or emetic) in the last 4 h and with mild-moderate state of dehydration were considered eligible for the study. Study subjects were allocated to two groups (group A, ginger or group B, placebo) according to a randomization list. The first dose of assigned treatment (20 drops per oral route = 10 mg of ginger or placebo) was given by the FPs at the enrolment; then, after thirty minutes children started oral rehydration according to ESPGHAN guidelines. Patients were prescribed to assume 20 drops of the assigned treatment every 8 hours until needed.

Results: 150 children were randomized, 75 per group; 9 subjects were lost to follow up, and 141 subjects completed the study: 70 in group A and 71 in group B. All children were from families of middle socioeconomic status and lived in urban areas. At baseline, main demographic and clinical features of the two study groups were similar. No child had received anti-Rotavirus or anti-influenza vaccine. The rate of subjects with ≥1 episode of vomiting after the first dose of assigned treatment was significantly lower in the subjects treated with ginger compared to placebo (66.7% vs 86.7% respectively, p<0.05). Starting from the first day of treatment the daily number of vomiting episodes was significantly lower in group A. The number of school days lost was significantly lower in children treated with ginger. Total diarrhea duration was similar into the two groups. No child required hospitalization. The intervention was well accepted by the children. No child presented adverse events.

Conclusion: The results of this study demonstrate that the oral administration of ginger in children affected by AGE is safe, well tolerated, and effective in reducing the duration and severity of vomiting. This is the first evidence in the pediatric setting and further RCTs are advocated to evaluate the effectiveness of this strategy in the treatment of vomiting induced by different etiology in children.
Butyrate has effects on intestinal smooth muscle adaptation in rats with massive small bowel resection

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Objectives and Study: Thickening of the intestinal wall, and lengthing of intestinal segments involves growth of intestinal smooth muscle cells (ISMCs), which contributes to structural intestinal adaptation in short bowel syndrome (SBS). Many studies have shown that butyrate not only has a trophic action, but also the immune-modulating and pro-proliferative activities. The purpose of this study was to investigate the underlying mechanisms of butyrate on ISMCs during intestinal adaptation in SBS.

Method: Sprague-Dawley rats were fed a fiber-free elemental diet and were randomly divided into three experimental groups: Sham group (rats underwent bowel transection and reanastomosis), SB W group (rats underwent 80% small bowel resection and received water), SB Bu group (rats underwent 80% small bowel resection and received 50mM sodium butyrate solution ad libitum after operation). The animals were weighed daily and tissue samples were harvested at day 7 and day 14 post-surgery. The length of residual small bowel was evaluated and the intestinal morpho-histochemical changes (villus height, circular and longitudinal muscular thickness, ISMCs proliferation, and ISMCs apoptosis) were determined. The role of yes-associated protein (YAP) was also analyzed by immunohistochemistry, qRT-PCR and Western blot. Meanwhile, human ISMCs were treated with butyrate solution (0.5mM), and cell growth was measured using direct cell count, CCK-8 assay, EdU incorporation assay, cell cycle analysis. Gene expression of YAP and its target genes were assessed using qRT-PCR. Subcellular localization of YAP were also analyzed by immunohistochemistry and Western blot.

Results: The body weight of the SB Bu group showed significant increases from postoperative day 3 to day 14, in comparison to that of the SB W group. The rats treated with butyrate had significantly greater villus height, circular and longitudinal muscular thickness, ISMCs proliferation, and both the mRNA and protein level of YAP and its downstream molecules in their residual intestines, as compared to the SB W group. A lower degree of ISMCs apoptosis was observed in rats treated with butyrate. In vitro studies demonstrated that butyrate promoted ISMCs, furthermore, the data indicated that the pro-proliferative effects of butyrate might be mediated via YAP activation and nuclear translocation.

Conclusion: These observations suggested that enteral butyrate supplementation promoted ISMCs proliferation and intestinal adaptive growth by activating YAP signaling pathway in SBS rats.
Butyrate supplementation promoted ISMCs proliferation and inhibited apoptosis.
Primary experience in safety and efficacy with duodenjejunal bypass liner in morbidly obese adolescents implanted for one year

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Objectives and Study: The duodenal-jejunal bypass liner (DJBL) (Endobarrier) is an endoscopic implant that mimics the duodenal-jejunal bypass component of the Roux-en-Y gastric bypass. Studies in adults have shown relevant weight loss and improvement in obesity related co-morbidities. The aim of this prospective study was to investigate for the first time in paediatric population (severely obese adolescents with obesity complications) safety and efficacy of DJBL 12 months after implantation.

Methods: The device was successfully implanted in 19 morbidly obese adolescents out of 22 who underwent the procedure (12 females, mean age 17.3 years (range 15.0 - 19.2); average BW 125.3 kg (range 93.2 - 158.8)). Inclusion criteria were: ≥ BMI 35 kg/m² with obesity complications such as hypertension, prediabetes, steatohepatitis. The metformin therapy was discontinued prior to DJBL placement. The exclusion criteria are described in detail at www.ClinicalTrials.gov (NCT02183935). The procedure was performed endoscopically under general anesthesia. Subjects were under observation in the hospital for 2 days following the procedure for possible complications. According to the protocol they were receiving esomeprazole 40 mg BID. The DJBL was removed endoscopically one year after implantation.

Results: In the safety analyses there were no severe procedure or post-procedure related complications. There were no cases of liver abscesses. Early device removal was not indicated in any of our patients. The most frequent adverse events were of gastrointestinal origin: nausea (14/19), abdominal pains (7/19), and vomiting (4/19) in the first two weeks after implantation. The constipation developed in 8 out of 19 adolescents throughout follow-up. One adolescent developed cholecystitis 3 months after endoscopy and two patients had transiently elevated pancreatic enzymes. The mean (±SEM) (BMI (kg/m²) was measured at 0, 3, 6, 9 and 12 months and decreased at all time frames (41.8 (±1), 39.4 (±0.8), 38.2 (±0.8), 38.2 (±0.9), 37.4 (±0.9), respectively). Furthermore, glucose metabolism significantly improved: mean HOMA-IR level at the beginning of the study was 5.3 (±0.5) and decreased at 6 and 12 months after implantation (3.8 (±0.4), 2.7 (±0.9), 3.4 (±0.4), respectively).

Conclusion: This is the first report of endoscopically placed DJBL in adolescents 12 months after implantation. The device has an acceptable safety profile in paediatric population. Furthermore, in the majority of children relevant weight loss was determined and glucose metabolism improved in all.

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Phenotypic variation in pediatric IBD by age: A multi-centre inception cohort study of the Canadian Children IBD Network

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Objectives and Study: The Paris classification of pediatric IBD divides “pediatric-onset” IBD (A1, Montreal classification) into A1a (diagnosis < 10 years (y)) and A1b (diagnosis ≥10 and< 17y). The Montreal A1 category was arbitrarily defined, but the Paris division was based on variation in spectrum of IBD localization with age, any ileal disease being uncommon prior to age 9-10y. Other variations in phenotypic spectrum with age have not been rigorously examined. The objective of the study was to examine the variation with age of IBD type, location, severity in a large national multi-centre prospectively accrued pediatric inception cohort of new onset IBD.

Method: Patients aged < 18y presenting with new onset IBD at 12 participating academic pediatric IBD centres were eligible for enrolment in an inception cohort study of the Canadian Children Inflammatory Bowel Disease Network, a joint partnership of the CIHR and CH.I.L.D Foundation (CIDsCaNN). Baseline and longitudinal phenotypic and demographic data were prospectively collected. Type of IBD was diagnosed as Crohn's disease (CD), ulcerative colitis (UC), or IBD type unclassified (IBDU) by the local site using conventional clinical, endoscopic and histologic criteria. Location was based on macroscopic disease as identified by colonoscopy and MR enterography. Disease activity at baseline and in follow-up was categorized by physician global assessment and measured by PCDAI or PUCAI, as appropriate. Mann-Whitney and Kruskal-Wallis tests were applied to determine statistical difference in the distribution by age at different age cut points.

Results: Between April 2014 and June 2017, 1146 children (median (IQR) age 13.2y (10.8:15.1); 56.5% male; CD:62%; UC:29%; IBDU:9%) were enrolled. Colon only disease (UC/IBDU or CD-colon) was the predominant IBD phenotype until diagnosis age 11y (p=0.004), with a progressive increase thereafter in the percentage children with any ileal or other small bowel CD (Figure 1). In the CD cohort overall, macroscopic location was 19%L1; 27%L2; 54%L3. L2 disease predominated until age 12y (p=0.001), when both L1 and L3 (any ileal disease) became more common. In the UC cohort the extent of disease was 9%E1; 6%E2; 11%E3; 74%E4; this distribution was consistent across all ages. The male:female ratio for the entire cohort was 1.3:1, and in both UC and CD, gender distribution was similar across all ages. Among children with UC, there was no variation in PGA of disease severity (mild:22%; moderate:42%; severe:34%; fulminant:2%) by age at diagnosis. In CD overall, severity was mild:26%; moderate:44%; severe:29%; fulminant:1%, but mild-moderate disease severity predominated until age 7y (p=0.01). Figure 1

Conclusion: Our data confirm the predominance of colon only IBD in younger children and support the Paris designation of A1a as early onset pediatric IBD. A spectrum of disease severity at diagnosis is seen across all ages.
Figure 1: Comparing age distribution of colonic only vs any ileal disease at diagnosis

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Clinical management of paediatric achalasia: a survey of current practice

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Objectives and Study: Paediatric achalasia is a rare neurodegenerative disorder of the oesophagus that requires treatment. Currently, there are no accepted recommendations for the clinical management of paediatric achalasia. We aimed to identify current practices regarding the diagnostic and therapeutic approach towards children with achalasia.

Method: Data regarding management of paediatric achalasia were collected by an online-based survey sent to members of the European and North American Societies for Paediatric Gastroenterology Hepatology and Nutrition involved in paediatric achalasia care.

Results: The survey was completed by 38 centres from 24 countries. Within these centres, 108 diagnoses of paediatric achalasia were made over the last year (median 2, range 0-15). Achalasia was primarily managed by a paediatric gastroenterologist (76%) and involved a multidisciplinary team in 84% of centres, also including a surgeon (87%), radiologist (61%) and dietician (37%). All centres used at least one diagnostic intervention as part of their work-up (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Europe (n = 17)</th>
<th>Asia (n = 8)</th>
<th>North-America (n = 6)</th>
<th>Australia (n = 4)</th>
<th>South America (n = 2)</th>
<th>Africa (n = 1)</th>
<th>Total (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of investigations</strong>&lt;br&gt;(median, range)</td>
<td>3 (1 - 5)</td>
<td>2.5 (2 - 4)</td>
<td>3 (2 - 5)</td>
<td>3 (3 - 5)</td>
<td>3</td>
<td>2</td>
<td>3 (1 - 5)</td>
</tr>
<tr>
<td><strong>Contrast swallow (n, %)</strong></td>
<td>14 (82%)</td>
<td>7 (88%)</td>
<td>5 (83%)</td>
<td>4 (100%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>33 (87%)</td>
</tr>
<tr>
<td><strong>Blood draw (n, %)</strong></td>
<td>6 (35%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td>2 (50%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td><strong>Conventional manometry (n, %)</strong></td>
<td>2 (12%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td><strong>High resolution manometry (n, %)</strong></td>
<td>12 (71%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td>2 (50%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>19 (50%)</td>
</tr>
<tr>
<td><strong>High resolution impedance manometry (n, %)</strong></td>
<td>2 (12%)</td>
<td>0 (0%)</td>
<td>5 (83%)</td>
<td>3 (75%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (26%)</td>
</tr>
<tr>
<td><strong>EGD (n, %)</strong></td>
<td>14 (82%)</td>
<td>8 (100%)</td>
<td>4 (67%)</td>
<td>3 (75%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>32 (84%)</td>
</tr>
<tr>
<td><strong>PH-MII (n, %)</strong></td>
<td>5 (29%)</td>
<td>2 (25%)</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td><strong>EndoFLIP (n, %)</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

(Table 1)
History taking and physical examination were considered most important to establish the diagnosis (50%), followed by (a combination of) manometry (45%) or (timed) barium swallows (21%). Respectively 47% and 24% of respondents indicated that patient's age and/or achalasia subtype would influence their primary choice of treatment. Treatment of first choice was Heller's myotomy (50%) which was available to 87% and routinely performed with a fundoplication as part of the operation in 52% of centres. Twelve centres (32%) performed at least one Heller's myotome (median 3, range 1-12) over the last three years. Pneumatic dilatation was indicated as treatment of first choice by 29% of respondents and available to 24/38 (63%) centres. Initial dilatation was performed with a balloon size ranging from 25-35mm and was repeated to up to 4 times in case of persisting symptoms with a maximum balloon size of 40mm. In six centres (25%), two dilatations were always performed regardless of symptoms. PerOral endoscopic myotomy was available to 29% of centres. Most respondents (84%) routinely performed post-intervention investigations, with follow-up varying from none to transition into adulthood. Thirty-seven percent of respondents indicated to prescribe anti-reflux therapy to all patients, regardless of the occurrence of symptoms.

Conclusion: This study shows a great heterogeneity in the diagnostic work-up and treatment of paediatric achalasia amongst different centres world-wide. These findings stress the need for clinical guidelines regarding diagnosis and therapy in children with achalasia. Given the rarity of this disease, we recommend that achalasia care should be centralized in centres with access to appropriate diagnostic and treatment modalities.

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Achalasia cardia subtypes on high resolution oesophageal manometry in children

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Objectives and Study: Achalasia cardia (AC) has been classified into three types by high resolution manometry (HRM) and this has a bearing on response to therapy in adults. Pediatric data is scarce. We evaluated children with AC by HRM to determine the prevalence of type I, II and III variants as well as differences in clinical profile and response to therapy between the subtypes.

Method: All children diagnosed as AC (clinical profile, timed barium oesophagogram [TBE], HRM and endoscopy) from 2012 to 2017 were evaluated. Patients with an adequate study i.e. ≥10 water swallows on HRM (22 channel water perfusion system, Solar GI, Medical Measurement System [MMS], The Netherlands) were enrolled. Subtype of achalasia was determined as per the Chicago classification. Clinical details including Eckhardt score, findings on TBE and HRM and post treatment outcome were noted. Pneumatic dilatation (PD) was done with 30 mm Rigiflex balloon (Microvasive, MA, USA).

Results: 26 children (14 boys, age 13.5±2.9 years, symptom duration 24.8±20.1 months) were enrolled. Dysphagia and regurgitation was present in all, followed by failure to gain weight (24, 92.3%), chest discomfort (12, 46%), pneumonia (2, 7.7%) and cough (2, 7.7%). Five (19.2%) cases had weight Z score of < -2 and 3(11.5%) had height Z score of < -2. One child had a lower esophageal diverticulum. Type I, II and III achalasia were present in 12 (46.2%), 13 (50%) and 1(3.8%) cases respectively. Overall, lower esophageal sphincter (LES) pressure was 29.1±11.7 and 4sec integrated relaxation pressure (IRP) was 29.4 ± 11.5 mmHg. PD was the primary therapy in 23 (88.5%) and Heller's myotomy in 3(11.5%) cases. One child with AC and extrahepatic portal venous obstruction with small varices was subjected to shunt surgery followed by Heller's myotomy. Table 1 shows the comparison between type I and II AC. Post PD (49.5±25.1 days) clinical evaluation showed that dysphagia was present in 4 cases (4/11 type 1 vs. 0/10 type 2; p=0.1). Post PD, HRM and TBE were available in 13 cases. Children with improvement on TBE (n=9) had lower LES pressure (11.1± 2.7 vs. 21± 3.3mmHg; p=0.001) than those with no improvement.

Conclusion: Type I and II achalasia are equally common, accounting for 97% cases in children. Type I and II AC are similar in clinical profile, however Type II has higher LES pressure and responds slightly better to PD than type I. TBE and HRM show good correlation post PD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type I (n=12)</th>
<th>Type II (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (y)</td>
<td>14±3.3</td>
<td>12.8±2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Boys (%)</td>
<td>4 (33.3)</td>
<td>9 (69.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>28.1±18.5</td>
<td>22.6±22.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Eckardt score</td>
<td>6.3±1.3</td>
<td>6.6±1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight Z score</td>
<td>-1.27±0.74</td>
<td>-1.34±0.73</td>
<td>0.8</td>
</tr>
<tr>
<td>4sec IRP(mmHg)</td>
<td>23.2±8.2</td>
<td>34.2±11.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal LES pressure (mmHg)</td>
<td>22.1±8.7</td>
<td>34.5±10.9</td>
<td>0.005</td>
</tr>
<tr>
<td>LES pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post PD(n=14)</td>
<td>11.6±4.2</td>
<td>14.3±6.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Post PD Eckhardt score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=21)</td>
<td>1.55± 1.8</td>
<td>0.40± 0.96</td>
<td>0.09</td>
</tr>
</tbody>
</table>

[Comparison between type I and II achalasia cardia]

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Safety of adalimumab in children and adolescents with moderate to severe Crohn’s disease: Interim results of the CAPE registry

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Objectives and Study: The 3-year safety and efficacy data of adalimumab (ADA) in children and adolescents with moderately to severely active Crohn’s disease (CD) enrolled in the IMAgINE 1 trial (N=192; ADA exposure, 151.8 patient-years [PYs]) was previously reported (Faubion, et al. IBD 2017). ADA long-term safety and effectiveness is currently being assessed in the postmarketing observational registry, CAPE. Interim safety data are reported herein.

Method: CAPE is a non-interventional, multinational, registry designed to include up to 10 years of routine clinical practice data on paediatric patients (6-17 years) with moderately to severely active CD treated with ADA (Humira®) or immunomodulator (IMM) monotherapy (azathioprine, mercaptopurine, or methotrexate). For this interim analysis at 3 years (started Aug 29, 2014), adverse events (AEs) were monitored through May 31, 2017. AE rates were assessed as events per 100 PYs (E/100 PYs) of ADA and IMM exposure, respectively. Registry treatment-emergent AEs (TEAEs) were defined as any AE occurring from the first dose of ADA or IMM in the registry through the last dose plus 70 days (ADA) or 30 days (IMM) or up to cut-off.

Results: 909 patients (ADA, N=518; IMM, N=391) were enrolled representing 378.8 and 328.2 PYs of exposure to ADA and IMM, respectively. 28 patients have withdrawn from the registry (ADA, n=13; IMM, n=15). At entry into CAPE, patient median (interquartile range) age was 15 (13-16) years and mean (SD) CD duration was 2.8 (2.46) years; the majority of patients are male (58.5%) and white (89.3%). TEAE incidence proportions and event rates per 100 PYs are shown in Table 1.

Table 1: Registry Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>ADA Registry Group N=518, 378.8 PY</th>
<th>IMM Registry Group N=391, 328.2 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Events (E/100 PY)</td>
</tr>
<tr>
<td>Any AE</td>
<td>59 (11.4)</td>
<td>129 (34.1)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>37 (7.1)</td>
<td>82 (21.6)</td>
</tr>
</tbody>
</table>
AE leading to discontinuation from registry | 1 (0.2) | 1 (0.3) | 0 | 0
---|---|---|---|---
Infection | 22 (4.2) | 30 (7.9) | 17 (4.3) | 22 (6.7)
Serious Infection | 13 (2.5) | 17 (4.5) | 9 (2.3) | 10 (3.0)
Intestinal stricture | 5 (1.0) | 5 (1.3) | 3 (0.8) | 5 (1.5)
Worsening/onset of psoriasis | 3 (0.6) | 3 (0.8) | 0 | 0

ADA, adalimumab; AE, adverse event; IMM, immunosuppressant; PY, patient year. *There were no incidences of death, opportunistic infection (excluding oral candidiasis and tuberculosis), tuberculosis, malignancies.

The rates of AEs and serious AEs (SAEs) were lower than the rates reported in the IMAgINE clinical trials. The majority of SAEs were associated with underlying CD in both registry groups. The most common serious infection (n [%]) was abdominal abscess in the ADA registry group (3 [0.6]) and gastroenteritis in the IMM registry group (2 [0.5]). There were no TEAEs of opportunistic infection, tuberculosis, malignancy, or demyelinating disorders reported in either registry group. Three cases of worsening/new onset of psoriasis were reported in the ADA group. No pregnancies or deaths were reported.

**Conclusion:** The safety of ADA observed in CAPE was comparable to its known benefit risk profile in children and adolescents with moderately to severely active CD, and no new safety signals were identified. Longer observation periods are needed to ascertain a more accurate risk of uncommon AEs.

**Disclosure of interest:** D Turner has received consultation fees, research grants, royalties, or honoraria from Janssen, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health, and Shire, during the last 3 years. S Koletzko has received consultancy fees from Abbvie, Biocodex, Boehringer Ingelheim, Danone, Janssen, Merck, MSD, Nestlé Nutrition, Menarini, and Shire; speaker fees from Abbvie, BerlinChemie, Danone, Hipp, Mead Johnson, MSD, Nestlé Nutrition, and Shire; and research support from BioGaia, Med Johnson, Menarini, Nestec-Nutrition, and R-Biopharm. HS Winter serves on the board of the Pediatric IBD Foundation (volunteer), Camp Jabberwocky (volunteer) and on Data and Safety Monitoring Boards for Crestovo and Janssen; acted as a consultant for Avaxia, Abbvie and Shire; received research grants from Abbvie, the Autism Research Foundation, Pfizer, Janssen, Nestlé, Nutricia, the Pediatric IBD Foundation, Shire, and UCB; provided expert testimony for Falk, Waas, Hernandez, Cortina, Solomon & Bonner, PA, Peabody & Arnold LLP, Post & Schell, P.C., and The Perry Law Firm; and has received royalties from UpToDate®. RN Baldassano has received consultancy fees from Janssen Ortho Biotech, AbbVie, Celgene, Pfizer, and Eli Lilly. M Dubinsky has received consultancy fees from Abbvie, Janssen, Takeda, UCB, Pfizer, Celgene, and Genentech. WA Faubion has received consultancy fees from Connecticut Children’s Medical Center—Safety Office on sub contracted award through NIH for clinical trial; serves as a board member (no personal compensation) for AbbVie and UCB; and serves as a consultant (no personal compensation) for AbbVie, Boehringer Ingelheim Pharma, Janssen Research & Development, Celgene Corporation, Genentech, and Shire Development. J Hyams has received consultancy fees from Janssen Ortho Biotech, AbbVie, Celgene, Enterra Health, Pfizer, Soligenix, Takeda, Lilly, Genentech, Boehringer Ingelheim, and AstraZeneca; provided expert testimony on behalf of Janssen Ortho Biotech; received speaker fees from Janssen Ortho Biotech; and received payment for development of educational presentations from Janssen Ortho Biotech. S Kugathasan serves as a consultant to Janssen, Takeda and Abbvie. J Rosh has received consultancy fees from AbbVie and Janssen; is a board member for GI Health Foundation; and has received financial support for research from AbbVie and Janssen. JC Escher has received consultancy fees from Janssen Ortho Biotech, AbbVie; speaker fees from AbbVie; and a research grant from MSD. AM Griffths has received consultancy fees from AbbVie, Nutricia, Janssen Canada, MSD, Ferring, and Shire; financial support for research from Johnson & Johnson, and AbbVie; speaker fees from AbbVie; and educational program support from AbbVie and Janssen Canada. J Kierkus has received consultation fees, research grants, or honoraria from Janssen, Abbvie, Takeda, Egis, Nestle, and Nutricia, during the last 5 years. RK Russell received consultation fees, research grants, royalties, or honoraria from Nestlé Health Science, AbbVie,
Celltrion, Shire, Janssen, and Therakos. GA Heap, D Arikan, V Kuehnl, J Petersson, and AM Robinson are AbbVie employees and may own AbbVie stock and/or options. FM Ruemmele has received speaker fees from Schering-Plough, Nestlé, Mead Johnson, Ferring, MSD, Johnson & Johnson, Centocor, and AbbVie; serves as a board member for SAC:DEVELOP (Johnson & Johnson); and has been invited to MSD France, Nestlé Nutrition Institute, Nestlé Health Science, Danone, and Mead Johnson.
Patterns of use and durability of initial and sequential biological agents in a large paediatric inflammatory bowel disease observational cohort

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Objectives and Study: Biological agents (BA) are indicated for treatment of children with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD). However, many children do not respond or lose response to BAs and require sequential biologic treatment. The aims of this study were to determine the frequency and patterns of initial and sequential BA use and BA durability in a large paediatric inflammatory bowel disease (IBD) cohort.

Method: We performed a retrospective study using data from ImproveCareNow (ICN), a multicenter prospective pediatric IBD registry. BA use and other clinical data were obtained directly from the ICN database. A subset of registry patients who were treated with their first BA after enrolment into ICN (chart review cohort), had additional clinical information obtained through chart review at 39 participating ICN sites.

Results: Of the 17,649 IBD patients (12,410 CD, 5,239 UC) diagnosed before 18 years of age, 7,585 (43%) were treated with a BA before age 18, including 50.5% of CD patients. CD patients were more likely to be treated with a BA than UC patients (odds ratio, 3.0; 95% confidence interval, 2.8-3.2; P < 0.0001) and patients diagnosed with CD between ages 6 and 11 were the most likely to be BA exposed (56.3%). Of all IBD patients currently < 6yo, 23.7% are BA exposed as are 41% of those aged 6-11 years. In the chart review cohort (n = 1029: 809 CD, 220 UC), the first BA was an anti-TNF agent in all cases (88% infliximab, 12% adalimumab). The median time from diagnosis to BA initiation was shorter in CD than in UC [325 vs 423 days; P = 0.004, Figure 1]. The probability of remaining on the first BA was higher in CD than UC [0.93 vs 0.84 at 6mo; 0.85 vs 0.75 at 12mo; 0.79 vs 0.66 at 24mo; 0.74 vs 0.55 at 36mo; P = < 0.0001]. The most common reasons for discontinuation of the first BA in all patients were secondary loss of response (39%), intolerance (23%) and primary non-response (PNR) (19%). PNR was a more common reason for discontinuation in UC than in CD (29% vs 15%, P = 0.02). Over a median follow up of 1.56 years [interquartile range, 0.89-2.57 years], 17%, 2.3%, and 0.6% of IBD patients were treated with at least two, three, or four BAs, respectively. The second BA was most often an anti-TNF agent (94.8%). Vedolizumab was the second BA in 4.6% of cases and the third in 37.5% of cases. In CD, the probability of remaining on the second BA was 0.95, 0.76, 0.72, and 0.64 at 6mo, 12mo, 24mo, and 36mo, respectively, while in UC the probability of remaining on the second BA was 0.85 at 6mo, 0.76 at 12mo and 0.65 at 24mo.

Conclusion: In this large paediatric-onset IBD cohort, BAs were used in >25% of children with UC and >50% of children with CD before 18 years of age. BA discontinuation and sequential BA treatment was relatively common. BAs were used earlier in disease course and the first BA was more durable in CD than in UC.
Disclosure of interest: This research was financially supported by Takeda. Trevor Lissoos: Employee, Takeda Pharmaceuticals, USA. Ashish Patel: Lecture Fees: Janssen, Abbvie, Abbott Nutrition Consultant; QOL. Richard Colletti: Financial Support of Research: Abbvie, Janssen Consultant: Abbvie, Janssen, Accordant Health Services

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Intestinal anti-tissue transglutaminase antibodies to simplify celiac disease diagnosis

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Objectives and Study: Anti tissue transglutaminase (anti-tTG) antibodies (abs) have simplified celiac disease (CD) diagnosis. However, intestinal biopsy is still required in atypical forms of CD. The aim of this prospective study was to investigate the presence of intestinal anti-tTG in patients with atypical forms of CD, and identify the most suitable detection test.

Method: Consecutive children undergoing upper gastrointestinal endoscopy (GE) were enrolled. The search of intestinal anti-tTG was performed in intestinal specimens comparing two immune-assays: the double-immunofluorescence for the detection of anti-tTG intestinal deposits and the intestinal biopsy culture for the measurement of both anti-endomysial (AEA) and anti-tTG abs in the supernatant.

Results: One hundred and thirty four patients were enrolled (79F-55M, median age 9±6y) and divided into 4 groups.
Group A: 71 patients, with CD suspicion and tested positive for HLA DQ2/8 and for serum CD abs, underwent GE. Histological analysis showed villous atrophy in all of them, intestinal IgA anti-tTG deposits were found in 71/71, and both AEA and anti-tTG IgA abs were tested positive in biopsy supernatant of 71/71. All these patients were diagnosed as CD patients and put in GFD. One/71 with IgA deficiency showed intestinal IgM anti-tTG deposits and, unexpectedly, AEA and anti-tTG IgA abs were measurable in the supernatant.
Group B: 8 patients, with CD suspicion and tested positive for HLA DQ2/8 and for serum CD abs, underwent GE. The intestinal mucosa was normal in all of them, intestinal IgA anti-tTG deposits were found in 8/8, and both AEA and anti-tTG IgA abs were tested positive in biopsy supernatant of 8/8. All these patients were diagnosed as potential CD patients and put in GFD.
Group C: 5 patients, with CD related symptoms and/or relatives of CD-patients, tested positive for HLA DQ2/8 and negative for serum CD abs and underwent GE. Histological analysis showed normal intestinal mucosa in all of them, intestinal IgA anti-tTG deposits were found in 5/5, and both AEA and anti-tTG IgA abs were tested positive in biopsy supernatant of 5/5. These patients were diagnosed as “pre-potential CD”, and 2/5 suffering from major symptoms (failure to thrive and anemia) were put in GFD improving their symptoms.
Group D: 50 patients underwent GE because suffering from other gastrointestinal disorders (control group) and 15/50 tested positive for HLA DQ2/8. Intestinal IgA anti-tTG deposits were not detected in 50/50, AEA IgA abs were not detectable in biopsy supernatant of 50/50 whereas anti-tTG IgA abs were tested positive in biopsy supernatant of 2/50.
Sensitivity of all the immune-assays is 100%; specificity of both intestinal anti-tTG and of AEA supernatant is 100%, and specificity of anti-tTG supernatant is 96%.

Conclusion: Intestinal anti-tTG abs are useful to identify “pre-potential CD” patients characterized by the absence of serum CD abs and of intestinal damage. For the first time AEA and anti-tTG IgA abs have been measured also in the biopsy culture of a patient with total serum IgA deficiency. The intestinal biopsy culture assay proved to be sensitive as the double immunofluorescence assay. Moreover, the intestinal biopsy culture assay simplifies the detection of intestinal anti-tTG abs and can be performed in non specialized centers.

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Differentiation of Colonic IBD: Re-examination of Porto algorithm with resected colon as gold standard

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Objectives and Study: Crohn's disease (CD) is differentiated from ulcerative colitis (UC) based on: symptoms, endoscopic appearances, mucosal pathology, and small bowel imaging, but labelling can be difficult when inflammation is predominantly colonic. Aiming to avoid variation in use of term Inflammatory bowel disease-unclassified (IBD-U), the Porto group of ESPGHAN developed an algorithm for labeling of IBD type (using 23 features clustered in 3 classes according to prevalence in UC cases), but based only on individual physician diagnosis of CD colon vs UC vs IBD-U as the gold standard. We aimed to assess the reliability and validity of the algorithm for the diagnosis of type of colonic IBD based on clinical data and endoscopically obtained mucosal biopsies, but using as gold standard expert pathologist examination of subsequent colectomy specimens.

Method: All pediatric patients < 18 yrs with colonic IBD undergoing colectomy at the Hospital for Sick Children, Toronto between 2002 and 2017 were included, provided diagnostic pre-treatment colonoscopy had been performed locally. Two reviewers (JD,FR) independently reviewed electronically stored pre-treatment data including symptoms, endoscopic appearances, mucosal biopsy and imaging reports, and serology in order to determine IBD type (CD/UC/IBD-U) based on Porto algorithm. Pre-colectomy clinical diagnosis and pathologist final diagnosis based on colectomy specimen were extracted. Concordance between algorithm-based label, pre-colectomy clinical diagnosis, and final histopathologic diagnosis was compared using kappa statistics. Changes in diagnosis during post-colectomy follow-up were recorded.

Results: 62 patients (median(IQR)age at diagnosis:12.9yrs(9.6,4.9); 50%male) underwent colectomy in the 15year period for medically refractory colonic IBD. Median(IQR) time to colectomy from diagnosis was 1.06yr(0.39,3.21). Ileoanal anastomosis with pouch procedure(IPPA) has hitherto been performed in 34 of 62 at a median of 35(25,54) weeks following colectomy. Gold standard diagnosis based on histopathologic review of resected colon was CD:2;UC:56;IBD-U:4. The clinical, algorithm-based, and colectomy histopathology-based diagnoses were concordant in 48(77%) of the 62 patients reviewed, Fleiss' Kappa=0.39. Patients with discordant labels are summarized in Table 1. Pre-colectomy clinical diagnosis differed from colectomy diagnosis in 12 patients(19.4%), (wkappa=0.31), including 7 patients labeled as IBD-U, whose colon pathology indicated UC. Clinical diagnosis differed from the algorithm-based label for 6 patients(9.7%), (wkappa=0.70) with algorithm less likely to diagnosis UC. Porto label differed from colectomy diagnosis in 14 cases(22.6%) (wkappa=0.29), including 8 patients labeled as IBD-U and 3 labeled as CD, whose colon pathology indicated UC. 4 patients with colectomy diagnosis of UC and 1 with colectomy diagnosis of IBD-U subsequently developed de novo signs of CD, all prior to IPPA and ostomy closure.

Conclusion: Concordance of full thickness colonic histopathologic diagnosis with pre-colectomy diagnosis using either Porto algorithm or clinical judgment is fair. Variation is mainly in direction away from diagnosis of definite UC pre-operatively. Observation of later de novo signs of CD justifies such pre-operative caution.
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<th>Pre-colectomy clinical diagnosis</th>
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* = at most recent follow-up, patient has not yet had IPPA with ostomy closure

[Table 1]
A randomized controlled trial comparing six-food elimination diet vs topical steroids in inducing and maintaining remission of paediatric eosinophilic esophagitis

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Objectives and Study: The current guidelines recommend topical steroids (fluticasone or budesonide) or elimination diet as first-line treatment for EoE. Unfortunately, there are no data comparing directly these therapies in children. The aims of this study is to assess the efficacy of 6-food elimination diet (SFED) and topical steroids in inducing and maintaining remission of paediatric EoE.

Methods: We prospectively enrolled active paediatric EoE patients during 2 years. At baseline children were randomized in four different treatments: SFED, swallowed fluticasone (SF), swallowed budesonide (SB) and oral viscous budesonide (OVB). The short- and long-term efficacy of each treatment was assessed by the percentage of responders (%/15/HPF of peak eosinophil count) after the induction therapy (8 weeks) and at the end of the study period (42 weeks). In the diet group, patients achieving remission after 8 weeks underwent systematic reintroduction of foods followed by endoscopy and biopsies, to identify the trigger foods. Whereas patients in remission with steroids continued the induction therapy until 12 weeks, before interrupting. In these patients, a second endoscopy could be performed between 26 and 30 weeks in case of symptomatic relapse. Patients with a histological flare-up were considered for a new treatment cycle with the same steroid of induction. All the patients received a final endoscopy at 42 weeks. Clinical symptom score (CSS), endoscopy (EREF score) and histology (count of eosinophils/hpf at all oesophageal levels) were evaluated at 0, 8 and 42 weeks.

Results: Of 74 patients evaluated, 64 were enrolled, but 50 completed the study and were considered for the final analysis. After induction therapy (8 weeks) the percentages of responders were 69%, 67%, 75% and 85% in the SFED, SF, SB and OVB, respectively. All treatments were able to significantly reduce the mean peak eosinophilic count compared to baseline (p<LT; 0.05). At the end of the study, the percentages of patients maintaining remission were 61%, 42%, 33% and 38% in the SFED, SF, SB and OVB, respectively. However, including and analysing also patients receiving a second steroids cycle at week 26-30 for a flare-up, the percentages of remission increased to 75%, 75% and 85% in the SF, SB and OVB, respectively (Figure). Based on reintroduction in the SFED group, the foods most frequently associated with EoE were milk (78% of cases) and egg (56% of cases).

Conclusions: This first paediatric, randomized controlled study on four different treatments shows that diet and topical steroids are both effective in inducing remission in paediatric EoE. Almost all children responders to diet maintained remission in the long-term follow-up by identifying the trigger foods. Topical steroids seem to have a higher efficacy in the short-term, but requires repeated cycles to maintain long-term remission.

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Cognitive debriefing interviews (phase 2B) towards developing a patient reported outcome for pediatric Ulcerative Colitis- the TUMMY-UC

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Objectives and Study: Under the qualification program of the FDA and EMA, we aimed to develop a Patient Reported Outcome (PRO) measure of signs and symptoms for pediatric ulcerative colitis (UC) (i.e. the TUMMY-UC index) for using in trials and clinical practice. We previously selected items to the index via concept elicitation qualitative interviews. Here we report the results of the cognitive evaluation and the final formatting of the index.

Method: Trained personnel performed Cognitive debriefing Interviews in Israel, England, Ireland, Canada and the USA with UC children 2-18 years and, in order to develop an Observer Reported Outcome (obsRO) for those ≤8 years, also their caregivers. We compiled contending scales for each item and explored the vocabulary children prefer. Clinical data including disease activity were recorded. Weights were assigned to each item based on ranking of importance on a ‘1’ (least important) to 5 scale.

Results: Interviews were performed with 34 children (age 10.6± 4 years; 28% with moderate-severe disease and 55% in remission; 83% with extensive disease) and 13 caregivers (age 37±5 years, 23% males). The questions were understood by all children and exact wording and response options of each item were finalized. 88% of children understood the meaning of “last 24-hours since this time” as a recall period. Only 3 children (9YO, 9YO, 12YO) had difficulties recalling the last 24-hours. The exact response options were amended based on the obtained feedback; all children < 11 years preferred the FACES pain item and most adolescents preferred the VAS version, thus both were retained in a composite item. Rank order of the items was: rectal bleeding-amount (4.5), rectal bleeding-frequency (4.3), stool frequency (4.2), abdominal pain (4), urgency (3.8), stool consistency (3.7), nocturnal stools (3.5) and weakness (3.2):
Reassuringly, the same rank-order was noticed for the children younger than 11 years.

**Conclusion:** In this phase 2B study, the exact wording, response options and weighting of the eight TUMMY-UC items were finalized. An obsRO version of the TUMMY-UC has been developed for the younger children. The TUMMY-UC will be now validated and evaluated for cutoff scores in a phase 3 study.

**Disclosure of interest:** This study has been funded by an educational grant from Janssen.

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Long-term maintenance therapy with the lowest effective dose of oral viscous budesonide in paediatric eosinophilic esophagitis

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Objectives and Study: Oral viscous budesonide (OVB) is efficacious in inducing and maintaining clinical/histological remission in paediatric Eosinophilic Esophagitis (EoE). However, it has not been established whether lowest effective dose might be identified, and whether treatment can be interrupted once patients have achieved remission after a history of frequent relapses. This study aims to identify the lowest effective dose of OVB by progressive halving dosage and to evaluate its efficacy on clinical, endoscopic and histological remission.

Methods: We prospectively enrolled active paediatric EoE patients (diagnosed according to the ESPGHAN criteria, J Pediatr Gastroenterol Nutr 2014;58:107-18) with an history of early relapse following topical steroids withdrawal (&LT; 6 months). Patients received a homemade suspension of OVB prepared by mixing inhaled budesonide with viscous solutions of sodium alginate (&LT; 150 cm: 0.5 mg bid; >150cm: 1 mg bid). After 12 weeks of induction therapy patients achieving a complete histological remission (a peak eosinophil count of &LT; 6/HPF in all esophageal levels) underwent a maintenance remission phase halving the dose every 24 weeks up to a minimum of 0.25mg/day and 0.125mg/day (single evening administration). Endoscopy was performed at 0,12,36,60 and 84 weeks. In case of symptomatic and/or histological flare-up, patients received a step-up therapy with the previous effective dose. Clinical symptom score (CSS) (Gupta SK, Clin Gastroenterol Hepatol 2015;13:66-76), endoscopy (EoE Endoscopic Reference Score, EREFS, modified; Gut 2013;62:489-95) and histology (count of eosinophils/hpf at all oesophageal levels) were evaluated. Serum cortisol was evaluated at baseline, 12,36,60 and 84 weeks.

Results: We enrolled 26 children (16 male, 10 female; median age 11 years, range 5-17). After 12 weeks of induction therapy with OVB, 23 patients (88%) were in clinical, endoscopic and histological remission. During the progressive halving therapy, remission was still observed in 21 (81%), 17 (65%) at 36 and 60 weeks, respectively. At the final 84-week assessment, 14 patients (54%) maintained remission by the lowest evening dose (0.25 and 0.125 mg/day). No significant difference in cortisol levels was observed during the study period. Only one oral candidiasis was recorded.

Conclusions: This first paediatric study on long-term maintenance therapy with OVB in paediatric EoE showed that a progressive dose reduction was effective in maintaining remission over 84 weeks. However, the lowest effective dose differs among patients and should be determined by halving the dose over the different follow-ups.

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Faecal calprotectin levels before and after exclusive and maintenance enteral nutrition in patients with active Crohn's disease. A dose-dependent effect of maintenance enteral nutrition?

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Objectives and Study: Exclusive enteral nutrition (EEN) is the first line treatment to induce remission in active luminal paediatric Crohn's disease (CD). Partial enteral nutrition as a maintenance treatment (MEN) of CD after EEN has been less well studied.

Method: Treatment naïve children with CD were prospectively recruited to the BIG (bacteria, inflammation & gastroenterology) study between August 2014 - April 2017. Patients were followed throughout their 8 week course of EEN. wPCDAI and faecal calprotectin (FC) were measured at baseline, 4 and 8 weeks on EEN and again at 15 and 60 days post-EEN. Those who successfully entered clinical remission (wPCDAI< 12.5) were offered MEN. Results are presented as median, Q1 - Q3 and FC in mg/kg. Low grade colonic inflammation was defined as FC < 250mg/kg.

Results: 72 patients were recruited who gave a total of 215 faecal samples; 67 started EEN [median age at EEN initiation 12.6y (10.4-16.5)]. The majority of patients were treated with polymeric feeds (Modulen=65); EEN was taken orally in 53 (79%) and via a nasogastric tube in 14 (21%). 42/67 (62.7%) entered clinical remission. FC decreased during EEN [EEN start: 1437.7 (912.7-1823.9) vs EEN end: 453 mg/kg (165-1183); p=0.001]. Importantly, in patients who entered remission, FC increased rapidly within 15d of returning to habitual diet [EEN end: 430 (141-1047) vs 15d post EEN: 907 (483-1487); p=0.032]. This increase continued and by 60d post-EEN median FC 1188 (732-1625) reverted to pre-EEN levels (p=0.101); Figure 1.
Of the 42 patients who entered remission, 29 (69.0%) used MEN, consuming a median of 400 ml (210-400) per day, equivalent to 18.8% (15.1%-30.1%) of their EEN energy requirements. 24/42 (57%) patients were on concomitant treatment with thiopurines at 15d and 60d post EEN. In group analysis, (MEN vs non-MEN users), FC levels were similar between the two groups at 15 days post-EEN (MEN=813 vs Non-MEN=1185; p=0.182). However when the volume of MEN was considered, an inverse relationship was observed between the volume (r=0.44, p=0.026) and kcals (r=0.40, p=0.001) from MEN and the rise of FC, 15 days post-EEN. All four patients with FC < 250 mg/kg at 15 days post-EEN were on high volumes of MEN. There was no association between FC levels and thiopurine use, perhaps unsurprising given the slow onset of action of these drugs.

**Conclusion:** FC significantly decreased during EEN but this effect reverted surprisingly quickly by 15 d of food reintroduction and vanished completely by 60 d. In MEN vs non-MEN group analysis there was no difference in FC but inverse relationships between volume and kcals consumed and FC suggest a dose-effect of MEN which warrants further exploration.

**Disclosure of interest:** KG received research grants, speakers fees and had conference attendance paid by Nutricia/Mead Johnson/Nestle. RH has received speakers/consultancy fees or conference support from Nutricia, Dr Falk, MSD Immunology and 4D Pharma. RKR has received speaker’s fees, travel support, and/or participated in medical board meetings with Nestle, MSD Immunology, AbbVie, Dr Falk, Takeda, Napp, Mead Johnson, Nutricia & 4D Pharma. RH & RKR are supported by an NHS Research Scotland Career Researcher Fellowships

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Prospective evaluation of intestinal damage in the development of coeliac disease in the
PreventCD cohort using circulating intestinal fatty acid binding protein


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Objectives and Study: The factors involved in the onset of coeliac disease (CD) development are not fully understood. It is hypothesized that intestinal mucosal damage is not only a disease consequence but might also be an etiological factor itself. Circulating intestinal fatty acid binding protein (I-FABP) concentration, a marker for enterocyte damage in the small intestine, is useful in assessment of disease activity in CD. We evaluated whether mucosal damage is present prior to CD autoimmunity (seroconversion) and can predict CD development, using serum I-FABP concentration as a marker. Secondly, the effect of gluten introduction herein was investigated.

Method: To investigate our aims, samples obtained from the preventCD study cohort were analysed. The preventCD project studies the influence of nutrition and other environmental factors, as well as the immunology and genetics involved in the development of CD in a European cohort of children with high risk for CD based on HLA genotype and at least one first-degree relative with CD. Subjects were followed from birth with blood sampling (www.preventcd.com). I-FABP was measured in a randomly selected subset of children of the preventCD cohort, 35 of which developed CD and 34 controls that did not develop CD within the follow-up period. Analysis included three time points, in sera from before and after gluten introduction and a fourth sample at CD seroconversion. Cases and controls were matched for age of sampling, sex, gender and HLA risk group. Data was pooled into time intervals of 6 months for statistical analysis.

Results: Within the chosen intervals, I-FABP levels did not differ between children that did or did not develop CD. However, I-FABP was significantly increased in sera within 6 months after gluten introduction in the children that developed CD as compared to controls (p=0.006). In the control group, a significant decrease of I-FABP after gluten introduction as compared to before gluten introduction was observed (p=0.013). Additionally, I-FABP was significantly increased in cases at diagnosis (p=0.001). I-FABP levels were notably high in the first three months after birth in both groups compared to samples taken at older age.

Conclusion: In subjects with a high risk for CD development, I-FABP is significantly increased in the first months after gluten introduction in children that will develop CD compared to those who did not. In children who did not develop CD, a significant decreases in I-FABP occurs over time. Moreover, in this group of high-risk subjects, I-FABP proves to be a useful additional marker to diagnose CD in young children at early stages of disease development. The evolution of I-FABP prior to seroconversion yields insights into the pathophysiological process of maturation and damage of the small intestine in children with high risk for CD development.
Factors associated with discontinuation of initial and subsequent tumour necrosis factor inhibitors in a large paediatric inflammatory bowel disease observational cohort

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Objectives and Study: Tumour necrosis factor inhibitors (TNFi) are effective in treating children with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD). However, nonresponse or loss of response to therapy may lead to sequential biologic treatment. Factors associated with TNFi discontinuation in children are not well known. The aim of this study was to assess for clinical factors associated with first and subsequent TNFi discontinuation in a large paediatric inflammatory bowel disease (IBD) cohort.

Method: We performed a retrospective study using data from ImproveCareNow (ICN), a multicenter, prospective paediatric IBD registry. Patients with CD and UC who were treated with their first TNFi following enrolment into ICN were identified at 39 participating ICN clinical sites. Clinical information was obtained from the ICN database and through chart review. The association of factors with TNFi discontinuation was assessed using Cox regression analysis.

Results: 846 patients (678 CD, 168 UC) who fulfilled inclusion criteria were identified. Infliximab (IFX) was used first in 89% of CD patients while 11% received adalimumab (ADA) first. Mean age at IBD diagnosis was 11.7 ± 3.4 years and mean age at TNFi initiation was 13.3 ± 3 years. At the time of first TNFi initiation, 64% (333/523) of CD patients had ileocolonic disease, 28% (175/623) had perianal involvement, 86% (557/649) had a non-penetrating, non-stricturing phenotype, and the mean shortPCDAI score was 24.2 (Table 1). For the UC patients, 79% (109/139) had pancolonic disease and mean PUCAI score was 35. Approximately half of UC and CD patients received at least a single thiopurine or methotrexate dose within the six months following the first TNFi start (Table 1). On univariate analysis, discontinuation of the first TNFi in CD was associated with colonic only vs ileocolonic disease location (hazard ratio [HR], 1.94; 95% confidence interval [CI], 1.28-2.94, P = 0.0020) and with higher shortPCDAI (HR, 1.01 per 1 unit increase in shortPCDAI; 95% CI, 1.00-1.02, P = 0.032) and prednisone use (HR, 1.49; 95% CI, 1.07-2.08, P = 0.017) at the time of TNFi initiation. Receipt of at least one dose of an immunomodulator in the 6 months following first TNFi initiation was not associated with TNFi discontinuation (P = 0.23). Discontinuation of the second TNFi (86% ADA, 14% IFX) in CD was associated with abnormal C-reactive protein (HR 3.33; 95% CI, 1.05-10.55, P = 0.041), lower albumin (P = 0.006) and hematocrit (P = 0.032) at the time of 2nd biologic initiation, and the presence of upper gastrointestinal (GI) tract CD (HR, 3.25; 95% CI, 1.13-9.35, P = 0.029). IFX was used first in 94% of UC patients, while 6% received ADA first. Discontinuation of the first TNFi in UC was more common with ADA compared to IFX (HR, 2.43; 95% CI, 1.02-5.80, P = 0.045).

Conclusion: Multiple factors associated with TNFi discontinuation in paediatric IBD patients were identified, including colonic only and upper GI tract CD location as well as markers of more severe CD at TNFi initiation like prednisone use and higher shortPCDAI. Prospective studies are needed to confirm these findings.
<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>CD (N=678)</th>
<th>UC (N=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First TNFi, infliximab (%)</td>
<td>88.5%</td>
<td>93.5%</td>
</tr>
<tr>
<td>Age at IBD diagnosis, years: mean (SD)</td>
<td>11.9 (3.2)</td>
<td>11.2 (4.1)</td>
</tr>
<tr>
<td>Age at first TNFi initiation, years: mean (SD)</td>
<td>13.4 (2.8)</td>
<td>13.1 (3.6)</td>
</tr>
<tr>
<td>ShortPCDAI score at TNFi initiation: mean (SD)</td>
<td>24.2 (18.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>PUCAI score at TNF initiation: mean (SD)</td>
<td>N/A</td>
<td>35.0 (23.9)</td>
</tr>
<tr>
<td>CRP at TNFi initiation, abnormal (%)</td>
<td>59.6%</td>
<td>40.3%</td>
</tr>
<tr>
<td>Perianal disease phenotype, (%)</td>
<td>28.1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Corticosteroid use at TNFi initiation, (%)</td>
<td>32.3%</td>
<td>56.5%</td>
</tr>
<tr>
<td>Immunomodulator use within 6 months following TNFi initiation, (%)</td>
<td>48.0%</td>
<td>50.9%</td>
</tr>
</tbody>
</table>

(Table 1)

Disclosure of interest: Trevor Lissoos: Employee, Takeda Pharmaceuticals Ashish Patel: Lecture Fees: Janssen, Abbvie, Abbott Nutrition, Consultant: QOL Richard Colletti: Financial Support of Research: Abbvie, Janssen, Consultant: Abbvie, Janssen, Accordant Health Services This study was financially supported by Takeda Pharmaceuticals

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High Prevalence of Common Congenital Sucrase-Isomaltase Deficiency Pathogenic Variants in Paediatric patients with Low Sucrase and Normal or Abnormal Lactase

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Background and study: Congenital Sucrase-Isomaltase Deficiency (CSID) impairs sucrase-isomaltase (SI) activity causing carbohydrate malabsorption, colonic fermentation, and symptoms of chronic diarrhea (CD), gassiness and/or abdominal pain (AP). Homozygosity and compound heterozygosity are associated with severe malabsorption. However, heterozygous mutations in those with depressed disaccharidases, with reduced sucrase, reduced maltase, normal lactase, and normal histology (NH) have been reported. We compared the prevalence of 4 common pathogenic variants using Next Generation Sequencing (NGS) of DNA from retrospectively available formalin fixed paraffin embedded (FFPE) tissue samples in cases with low sucrase, and normal or abnormal lactase, and controls with high-normal sucrase.

Hypothesis: CSID pathogenic variant carrier frequencies are higher in cases with low sucrase activity.

Methods: An IRB approved retrospective case-control study was conducted. Low sucrase cases and race-matched controls and moderates were identified from electronic records with clinical histories. Using stored formalin fixed paraffin embedded (FFPE) tissue samples, the frequency of known pathogenic CSID and exploratory SI-exon variants was determined in patients with low, high, and moderate sucrase activities (Table 1). The NGS method was optimized with FFPE tissue DNA for Illumina's MiSeq platform using custom amplicon design targeting the SI-exons. Cases (n=125) were Caucasian patients with a symptom complex including CD and/or AP, NH, low sucrase (≤55U), no known organic GI disorder, and with or without low lactase (≤15U). Controls (n=250) and moderates (n=189) were Caucasian patients with high (>55U) and moderate (>25–≤55U) sucrase activities, NH, and no organic GI disorder.

Results: The average disaccharidase activities were low in cases (Table 1). Three of the top 4 known CSID pathogenic variants were detected in 20/125 cases (all heterozygous), 0/250 controls and 4/189 moderates (Table 1). The top 4 known pathogenic CSID variant carrier frequency in cases was significantly greater (p=< 0.001) than in controls & moderates (Table 2). Cases with GI symptoms and sucrase deficiency were 14.1 times (95% CI 23.0, 8.7) more likely to have top 4 known pathogenic CSID variants than the Exome Aggregation Consortium (ExAC) general population database. Cases with both normal / abnormal lactase (p=< 0.001) had statistically significant high CSID carrier frequencies (Table 2). Sucrase deficiency is the key phenotype that correlates better with CSID genotype (Tables 3 & 4).
Conclusions: In patients with chronic diarrhea and or abdominal pain with low sucrase and normal histology, SI-exon variant detection with FFPE samples using NGS shows a higher rate of pathogenic variants than controls, implicating genetic basis of malabsorption of sugars and starches. Overall, in symptomatic Caucasian patients, 3 common pathogenic SI variants were found in up to 16% of patients, even with co-existing lactase deficiency. Given the recognized top CSID pathogenic variants were detected at a much higher frequency in cases vs. controls or moderates, heterozygosity with pathogenic variants are implicated in causing symptoms. Further analysis with all confirmed variants will be presented.

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Gastroenterology - Basic science

G-eP-002

Preterm birth induces persistent delay in gut and immune maturation in the postnatal period of pigs

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Objectives and Study: The adaptation and maturation of immature organs following preterm birth may be associated with increased risks of infection and organ dysfunctions. Using preterm pigs as a model for preterm infants, we compared the maturational trajectory of gut functions and systemic immunity between preterm and term neonates. We hypothesized that these maturations depend more on changes in the external environment (e.g. birth, nutrition, microbes, postnatal age, PNA) than on age after conception (post-conceptional age, PCA).

Method: Pigs were delivered by Caesarean section at d 106 (preterm, n=43) and d 116 of gestation (term, n=41) and euthanized for tissue collection at birth (d 1) or d 11. Postnatally, pigs were fed the same amount (per kg) of parenteral nutrition and enteral nutrition (gradual transition from bovine colostrum to mature milk). Values were compared between preterm and term pigs both at the same PNA (d 1 and 11) and PCA (preterm d 11 vs. term d 1).

Results: At the same PCA, all investigated organs, except the brain, showed different levels of maturation between preterm and term pigs. For example, preterm pigs on d 11 showed greater relative gut weight, gut cytokine IL-1β levels, sucrose and maltase activities but shorter villus height, lower goblet cell density and lactase activities than term pigs on d 1. Similarly, preterm pigs on d 11 showed greater levels of blood leukocytes, neutrophils and neutrophil phagocytic function but lower levels of blood cytotoxic T cells and NK cells than term pigs on d 1. In contrast, brain weight was closely related to PCA, with weights being identical between d 11 preterm and term newborn pigs. When comparing preterm and term pigs at the same PNA, preterm pigs showed delayed maturation shown by multiple parameters including lower growth rate, cord plasma cortisol and cortisol response to ACTH. Relative gut and brain weight, villus height, gut I-FABP levels and disaccharidase activities increased with advancing PNA but remained at lower levels in preterm than term pigs on d 1 and/or d 11. Gut permeability decreased over time but remained higher in preterm than term pigs at both PNA. Blood leukocyte and neutrophil numbers were lower in newborn preterm vs. term pigs, but increased to similar levels between groups by d 11. In contrast, the proportion of blood NK cells and cytotoxic T cells were lower in preterm than term pigs on both d 1 and 11.

Conclusion: Gut and immune parameters were immature in preterm vs. term pigs at birth and did not develop according to PCA. Some parameters showed a persistent delay in structural and functional maturation in preterm animals, relative to term animals at the same PNA. Our data suggest a highly distinct trajectory of gut and immune development during the first weeks of life in preterm neonates. Factors related to the birth transition and environment (e.g. nutrition, microbes) may determine gut and immune development in preterm neonates, rather than advancing PCA before or after birth. Conversely, PCA may mainly determine development of organs such as the brain that is relatively protected from the external environment. Relating postnatal maturation of preterm infants to their PCA is highly organ-specific and a poor measure of overall physiological maturation.
A

**STUDY DESIGN:**

**TERM**

- d1 Postnatal age (PNA) d11

**PRETERM**

- d1 Postnatal age (PNA) d11
- d106
- d117
- d128

**Post-conceptional age (PCA)**

B

**Relative small intestinal weight**

[Study design and relative gut weight. Postconceptional- vs. postnatal ages of preterm and term pigs]

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Modulation of Intestinal Serotonin Production and Serotonin Transporter by Lactobacillus reuteri and Bifidobacterium dentium

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Objectives and Study: The metabolite and neurotransmitter serotonin (5-HT) has a diverse physiological repertoire. In the gut, 5-HT modulates intestinal fluid secretion and gut motility. Dysregulation of 5-HT and its transporter, SERT, have been implicated in a number of gastrointestinal disorders including inflammatory bowel disease (IBD). We hypothesized that select Lactobacillus and Bifidobacterium strains would stimulate 5-HT production and upregulate SERT.

Method: Twenty-four Lactobacillus and one Bifidobacterium strains were cultured anaerobically in a fully defined media (LDM4) and 5-HT production measured by MS/MS analysis. The human intestinal cell lines, HT29, were exposed to lactic acid bacteria conditioned media and/or IL-1β for 30 min to 24 hrs and SERT expression was analyzed by qRT-PCR. 5-HT and SERT protein abundance and localization were examined by immunofluorescence. Magpix Protein Analysis of Phosphorylated MAPK molecules was used to determine the signal involving in SERT regulation. To address 5-HT production in vivo, germ-free mice were colonized with B. dentium or L. reuteri as well as ileum and colon luminal 5-HT levels were examined via ELISA. Mouse intestinal SERT expression was examined by qRT-PCR.

Results: Of the 24 Lactobacillus and one Bifidobacterium strains examined, none produced bacterial 5-HT as determined by MS/MS analysis. Incubation of L. reuteri and B. dentium conditioned media (CM) with human epithelial HT29 cells revealed significant increases in SERT after 12 hr culture, with maximum upregulation at 24 hr as assessed by qPCR and immunofluorescence (IF). Additionally, L. reuteri and B. dentium CM stimulated activation of ERK and JNK pathways in HT29 cells. No changes were observed in p38, STAT3, STAT5 or NFκB activation. Incubation of CM with mouse ileal enteroids mirrored this effect, with localized upregulation of SERT and secretion of 5-HT. To address 5-HT production in vivo, germ-free mice were colonized with B. dentium or L. reuteri. B. dentium treated mice exhibited increased luminal 5-HT in the ileum and increased blood 5-HT compared with controls. In mouse ileum and colon, SERT was found to be present on enterochromaffin cells (EECs) and on the basolateral membrane of neighboring epithelial cells. L. reuteri and B. dentium mono-associated mice exhibited increased numbers of EECs expressing 5-HT, demonstrating that lactic acid bacteria colonization can promote 5-HT production.

Conclusion: These data indicate that commensal microbes, L. reuteri and B. dentium, are capable of modulating key components of the intestinal serotonergic system. As downregulation of SERT has been implicated in the pathophysiology of several functional gut disorders, our data supports consideration of next generation probiotics as therapies for 5-HT-associated disorders.

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Distribution and phenotype of tissue-resident memory T cells in children gastrointestinal mucosal tissue

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Objectives and Study: Mouse studies indicate that tissue localization of T cell subsets is important for both protective immunity and immunoregulation in the gastrointestinal disease. In human child, the differentiation and distribution of tissue resident memory T cell (TRM) in gastrointestinal mucous remain poorly defined. We present here a quantitative analysis of human T cell compartmentalization and phenotype in alimentary canal tissues obtained from children donors.

Method: Through the Institutional Review Board of Guangzhou Women and Children’s Medical Center, we have obtained mucosal tissues (including esophagus, stomach, duodenum, ileum, colon and rectum) from a highly diverse cohort of 251 children donors aged 1-14 years. The 251 individuals used for this study are highly diverse, ranging in age from 1-14 years. All mucosal biopsies were healthy and excluded pathological tissue by histopathology examinations. Mucosal biopsies were washed with PBS+EDTA, and then digested with collagenase D and DNase I. Biopsies were homogenized in blullet blender, and cell suspension was collected and passed through cell strainer. The resulting cells were counted and used in 7 colors panel surface staining (including CD3, CD4, CD8, CD69, CD103, CD45RO and CCR7). Flow cytometric analysis was performed on FACS BD LSRFortessa, and data were analysed using FlowJo software.

Results: Samples from upper gastrointestinal (including esophagus, stomach and duodenum) contained lower CD4⁺ and CD8⁺ T cell ratios than those from lower gastrointestinal (including ileum, colon and rectum). Among samples from lower gastrointestinal, distal ileum contained most frequencies of CD4⁺ and CD8⁺ T cells, following by colon. From age 1 to 14 years, the frequencies of tissue resident CD4⁺ and CD8⁺ T cells increased in an aged-dependence. Tissue resident phenotype analysis revealed that most CD8⁺ T cells in mucosal tissue co-expressed CD103 and CD69 (86.5±8.6%), while a much lower percentage of CD4⁺ T cells co-expressed these markers (24.4±9.8%). Expression of CD69 alone was found in about 52% of CD4⁺ T cells. Memory phenotype analysis revealed that TEM (CD45RO⁺CCR7⁻) subset of CD4⁺ and CD8⁺ T cells predominated in all mucosal sites (85.2±10.2%), while lower percentage of naive (CD45RO CCR7⁻) and TCM (CD45RO⁻CCR7⁻) comprised only 5-15% of T cells. Moreover, tissue resident and memory phenotypes of T cells were similar in different parts of gastrointestinal. The frequencies of TEM and CD69⁺CD103⁺ subsets in CD4⁺ T cells increased gradually from age 1 to 14 years, while no significant difference was observed in CD8⁺ T cells in different age.

Conclusion: The study demonstrates the distribution of CD4⁺ and CD8⁺ T cells in whole gastrointestinal tissue of children from age 1 to 14 years, which exhibit diverse functional phenotype. The study describes a spatial and temporal map of tissue resident memory T cell in children gastrointestinal tissue, which provides a new baseline for understanding human adaptive immunity associated with gastrointestinal disease.
[Distribution and phenotype of tissue-resident memory T cells in children gastrointestinal mucous]

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Predictive factors on outcomes in paediatric Crohn’s disease: a systematic review

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²Hospital for Sick Children, Toronto, Canada
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Objectives and Study: Paediatric-onset Crohn’s disease (CD) encompasses a spectrum of phenotypes and disease severity. Risk stratification to facilitate early, more individualized therapy is key to optimizing outcomes. We aimed to systematically review the evidence pertaining to the prediction of chronically active inflammatory activity and disease complications in paediatric CD.

Method: A systematic search in Pubmed and EMBASE was performed, including paediatric observational or controlled studies reporting longitudinal associations between patient- or disease characteristics and complications of CD or chronically active inflammatory disease. Complications included: stricturing (B2), penetrating (B3) or perianal disease, linear growth impairment, bone disease, surgery, disease extension and poor response to therapy or need for more intensive therapy. Studies were included if published from 1992 to June 2017 and written in English. Study selection was performed by 2 reviewers. Risk of bias was assessed with the Newcastle-Ottawa tool. A random effects model was used to perform a meta-analysis on predictors.

Results: The search identified 97 eligible studies (all observational). The majority focused on patient or disease characteristics associated with surgery (n=46), stricturing (n=32) or penetrating complications (n=30). Others investigated associations with growth impairment (n=20), perianal fistulizing disease (n=19), chronically active inflammatory disease (n=9) or bone disease (n=10). In a pooled analysis, non-Caucasian ethnicity was found to be a risk factor for B2 and/or B3 complications with a relative risk (RR) of 2.90 (95% CI 1.77-4.77) and isolated small bowel disease (L1) was associated with an increased risk of stricturing complications (RR 2.09; 95% CI 1.46-2.98). ASCA IgA positivity and positivity for any antimicrobial serology were associated with the outcomes of B3 complications (RR 3.66; 95% CI 2.13-6.27), and B2 and/or B3 complications (RR 3.00; 95% CI 1.36-6.62), respectively. Across several studies, CBir1 had aHRs of 2.3 to 3.0 for B2 and/or B3 disease. The presence of at least one NOD2/CARD15 variant was found to be a risk factor for stricturing disease (RR 2.62; 95% CI 1.62-4.25), but not penetrating disease (RR 1.44; 95% CI 0.85-2.45) based on a pooled analysis of 9 studies including 1060 children. Across several studies, male sex was associated with HRs of 3.6 to 3.9 for linear growth impairment. Lower weight, lower body mass index and more active disease were associated with lower bone mineral density over time. Table 1 lists factors for which at least one study reported an association with an outcome of interest. The number of studies demonstrating a significantly positive (+) or negative (-) association, amongst all studies examining the predictor, is shown in brackets. No clear risk factors were identified for hospitalization and chronically active inflammatory disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Demographic associations</th>
<th>Phenotypic associations</th>
<th>Serologic and genetic predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of B2 disease</td>
<td></td>
<td>L1 ± L4b (1/3 +)</td>
<td>Antimicrobial serologies (1/2 +)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NOD2/CARD15 polymorphisms (4/12 +)</td>
</tr>
<tr>
<td>Development of B3 disease</td>
<td>Older age (2/4 +) Non- Caucasian ethnicity (2/2 +)</td>
<td></td>
<td>Antimicrobial serologies (2/3 +)</td>
</tr>
<tr>
<td>Development of B2 and/or B3 disease</td>
<td>Non-Caucasian ethnicity (1/1 +)</td>
<td>L1 ± L4b (1/4 +)</td>
<td>Antimicrobial serologies (3/3 +)</td>
</tr>
</tbody>
</table>
**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perianal fistulizing disease</strong></td>
<td>Older age (3/3 +) Non-Caucasian ethnicity (2/2 +)</td>
<td></td>
</tr>
<tr>
<td><strong>Linear growth impairment</strong></td>
<td>Male sex (4/9 +) Younger age (4/8 +) Diagnostic delay (2/4 +)</td>
<td>L1 ± L4b (3/7 +) Disease activity (6/8 +)</td>
</tr>
</tbody>
</table>

**Conclusion:** The majority of identified predictors are observed demographic or phenotypic associations. To date, only antimicrobial serology provides additional guidance for individualizing treatment based on risk prediction. Molecular predictors of chronically active inflammatory disease and biologic treatment responsiveness are badly needed.

**Disclosure of interest:** Disclaimer: This abstract has been developed subsequent to an AbbVie sponsored literature review on prognostic factors in PIBD, however, AbbVie was not involved in the development of the abstract. AbbVie selected the discussion participants and reviewed the draft for scientific accuracy, but the authors determined the final content.

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Upper GI endoscopy is an expensive accessory investigation in the diagnosis of Crohn's disease in children

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Objectives and Study: ESPGHAN Porto revised criteria recommends upper gastrointestinal endoscopy (OGD) and ileo-colonoscopy with small bowel imaging for all suspected patients with Crohn's disease (CD). OGD is recommended with an aim to improve the diagnostic yield in patients suspected to have Crohn's disease (CD). The aim of this project is to analyse the additional diagnostic yield gained from OGD in patients who had diagnostic colonoscopy for suspected IBD.

Method: We have done a retrospective analysis of the data of 100 consecutive CD patients diagnosed in the time period of 2013-2017. All these patients had OGD and colonoscopy. Endoscopy reports and histological reports were reviewed. We have analysed the cost of OGD in these patients.

Results: Out of 100 CD patients (L1 33%, L2 36%, L3 31%) who underwent both OGD and colonoscopy, 52 colonoscopies and 34 OGD were diagnostic macroscopically (Ulcers typical of Crohn's disease were seen). Ileal intubation rate was 80%. Histology was diagnostic of CD in 76% colonoscopies and 41% of OGDs. Of the 48 patients in whom colonoscopies were non-diagnostic macroscopically, only 15 patients (31%) had macroscopic abnormalities of Crohn's disease in OGD. All patients who had diagnostic colonoscopy features of Crohn's disease, histology was confirmative of CD. Of the 48 patients who had non-diagnostic colonoscopy appearance of CD, 33 had diagnostic histology of CD. Only 2 patients had diagnostic histology from OGD out of the 15 patients who had non-diagnostic histology from colonoscopy. In summary OGD provided additional diagnostic yield only in 2% patients (picture 1). Approximately 75,000 Euros could have been saved by avoiding OGD in 85% of these patients (average cost of diagnostic OGD is €880/-)

Conclusion: 85% of patients with Crohn's disease can be diagnosed by colonoscopy and histology. OGD provided additional diagnostic yield in only 2% patients with Crohn's disease.

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Trends in epidemiology of inflammatory bowel disease among adolescents in Israel: A population based study

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Objectives and Study: Several studies have demonstrated an increasing prevalence of paediatric Inflammatory bowel disease. However, relatively little is known about paediatric inflammatory bowel disease epidemiology in Israel. We aimed to investigate the prevalence and sociodemographic factors associated with diagnosis of inflammatory bowel diseases among Jewish Israeli adolescents.

Methods: A total of 1,144,213 Jewish Israeli adolescents who underwent a general health examination from 2002 to 2016, at a median age of 17.1, were included. Cases were classified into Crohn’s disease and ulcerative colitis. Covariate data included date of birth, country of birth, parental country of birth, age at diagnosis and socioeconomic status.

Results: Overall, 2,372 cases of inflammatory bowel disease were identified (0.2%). Crohn’s disease accounted for 68% of cases. Total inflammatory bowel disease point prevalence increased from 58 per 100,000 persons per year to 373 per 100,000 persons over the study period. This increase was observed for both Crohn’s (from 42 to 245 per 100,000 persons per year) and ulcerative colitis (from 16 to 128 per 100,000 persons per year, as demonstrated in figure 1. The mean age of inflammatory bowel disease diagnosis decreased from 14.97 years of age during the years 2002-2008 to 14.32 during 2009-2016 (p< 0.0001). Significance was maintained for both diseases.

Compared with Israeli origin, both Crohn’s disease and ulcerative colitis diagnosis were significantly less prevalent in subjects whose one of their parents was born in Asia, Africa and Ethiopia. Western origin of either parents was associated with increased risk only for Crohn’s. Lower sociodemographic status was also significantly associated with lower prevalence (odds ratio of 0.25 for low status for both diseases).

Conclusion: The prevalence of both Crohn’s disease and ulcerative colitis significantly increased during the study period. Average age at diagnosis decreased during our study period for both diseases. Higher sociodemographic status is a significant independent risk factor for both ulcerative colitis and Crohn’s disease.
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Variation in classification of pediatric inflammatory bowel disease in a multi-centre inception cohort

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Objectives and Study: Differentiation of Crohn's disease (CD) from ulcerative colitis (UC) can be difficult when inflammation is predominantly colonic; the term Inflammatory Bowel Disease unclassified (IBD-U) is utilised when features of both exist. In a large multi-centre study, using as gold standard physician diagnosis of CD colon vs UC vs IBD-U, the Porto Group of ESPGHAN developed an algorithm (23 features clustered in 3 classes according to prevalence in UC cases) aiming to bring consistency to the assignment of type of colonic IBD. In a Canadian multi-centre inception cohort study, we aimed to assess variation among IBD specialists in the classification of predominantly colonic IBD with and without the algorithm.

Method: The Canadian Children IBD Network enrols children aged < 18yrs newly diagnosed with IBD at 12 pediatric IBD centres. Anonymized data including baseline endoscopy, pathology, imaging and serology are uploaded into a on-line database. Three central reviewers (JC;AG;HH) independently assign type of IBD (UC;CD;IBD-U). Restricting to patients with predominantly colonic IBD, concordance among reviewers was assessed using kappa statistics. Two reviewers (JD;NC) independently applied the algorithm using the same phenotypic data. Concordance among central reviewers, local site and the Porto algorithm was assessed using kappa statistics. Features contributing to discordance were determined. Participating sites provided information concerning any change of diagnosis during follow-up.

Results: The 3 central reviewers independently assigned a concordant diagnostic label for 97(95%) of 102 patients. Two of 3 were concordant for an additional 5 (5%), overall kappa=0.93. Central consensus diagnoses were:CD:56,UC:39,IBD-U:7. The local site, central consensus and algorithm diagnosis were concordant for 83(81%) of the 102 patients, Kappa=0.751. Of the 19 patients lacking concordance for CD vs IBD-U vs UC, patients 1 to 10 were discordant for the label of CD vs UC/IBD-U (Table). For 5 of these 10, central consensus and algorithm diagnoses were concordant, but differed from the initial local site diagnosis on which treatment decisions were made. Overall, site diagnosis differed from the central consensus label for 13 patients (12.7%), (wkappa=0.86), central consensus from the algorithm for 12 patients (11.8%), (wkappa=0.88), local site from algorithm for 17 patients (16.7%), (wkappa=0.77). As shown in Table, most discordance between central consensus and algorithm-based diagnoses is attributable to consensus acceptance of UC diagnosis (n=8) despite presence of one class 2 feature or of IBD-U diagnosis (n=3) despite presence of one class 1 feature including a single granuloma in upper GI tract (n=2). Interpretation of colonic skip lesions led to inconsistencies in the remaining two cases.

Conclusion: Labelling of predominantly colonic IBD is challenging. Algorithm-based assignment of type of IBD is more concordant with central consensus diagnosis than with local site diagnosis, suggesting that following algorithm might help individual sites reach more consistent label. Consensus labelling of UC and IBD-U, however, does dispute rigid interpretation of single class 2 or single class 1 features, respectively. Further validation of algorithm based on superior gold standard is needed.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial local site label</th>
<th>Central consensus label</th>
<th>Algorithm-based label</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD</td>
<td>UC</td>
<td>UC</td>
</tr>
<tr>
<td>2</td>
<td>CD</td>
<td>IBD-U</td>
<td>IBD-U</td>
</tr>
<tr>
<td>3</td>
<td>CD</td>
<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
<td>4</td>
<td>CD</td>
<td>CD</td>
<td>IBD-U</td>
</tr>
<tr>
<td>5</td>
<td>IBD-U</td>
<td>CD</td>
<td>CD</td>
</tr>
<tr>
<td>6</td>
<td>CD (IBD-U in follow-up)</td>
<td>IBD-U</td>
<td>IBD-U</td>
</tr>
<tr>
<td>7</td>
<td>UC</td>
<td>IBD-U*</td>
<td>CD</td>
</tr>
<tr>
<td>8</td>
<td>IBD-U</td>
<td>CD</td>
<td>CD</td>
</tr>
<tr>
<td>9</td>
<td>UC</td>
<td>IBD-U*</td>
<td>CD</td>
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<td>10</td>
<td>UC (CD in follow-up)</td>
<td>IBD-U*</td>
<td>CD</td>
</tr>
<tr>
<td>11</td>
<td>UC</td>
<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
<td>12</td>
<td>UC</td>
<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
<td>13</td>
<td>UC</td>
<td>UC +</td>
<td>IBD-U</td>
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<td>UC</td>
<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
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<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
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<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
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<td>UC +</td>
<td>IBD-U</td>
</tr>
<tr>
<td>18</td>
<td>UC</td>
<td>IBD-U</td>
<td>IBD-U</td>
</tr>
<tr>
<td>19</td>
<td>IBD-U</td>
<td>UC</td>
<td>UC</td>
</tr>
</tbody>
</table>

* despite one class 1 feature + despite one class 2 feature

[Table 1]
GASTROENTEROLOGY - Inflammatory bowel disease

G-eP-009

Quality of life reported by Italian children with IBD and their parents: preliminary results of a multicenter SIGENP study

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Objectives and Study: Quality of life (QoL) is a well-established target of IBD care. We aimed to evaluate: 1. concordance between parents and child ratings of QoL, 2. patients and disease features contributing to QoL.

Method: The IMPACT-III questionnaire was administered to IBD children (8-18 years) and one of their parents in 7 Italian centers. Correlation between parent and child QoL scores and associations between QoL and patient's characteristics and disease features were calculated.

Results: A total of 192 children with IBD (median age 15 years IQ range 12.15-16.63, 54.7 % boys, 54.1% CD, 44.3% UC, median duration of disease 10.8 years, IQ 7.86-13.32) and one of their parents (78.7 % mothers) have been enrolled so far. 73% were in clinical remission, 31.7% had at least one clinical relapse in the last year. Median QOL score was 67.8 (IQ range 42.5-81), a significant difference was found between the scores in each domain (p= 0.0016), with the lowest score found in the “body image domain” (58.3 IQ range: 41.6-75) and the highest in the “bowel symptoms domain” (78.57, IQ range 39.3-89.3). Parent-proxy and patient ratings were similar on total IMPACT III and its related domains (p=ns) and no difference was detected between mothers and fathers' scores. QoL (total score and related domains) was not found to be related to age, sex and disease type. QoL scores were significantly higher in IBD children from north Italy compared to children from south and central Italy (p &LT; 0.0001 in all the domains). The overall QoL score was positively correlated to disease duration (r= 0.16, p= 0.024). A significant lower QoL was found in patients with moderate/severe activity compared to patients in remission or mild activity, defined both by PGA (p=0.007) or by disease's activity scores PCDAI/PUCAI (p=0.024). A significant inverse correlation was found between fecal calprotectin levels and total QoL score (r= -0.32, p=0.0014). Current use of biologics was correlated to a lower total QOL score (p &LT; 0.0001). Results of the multiple regression analysis (variables included: disease activity, length of disease, fecal calprotectin levels, use of biologics, geographical provenience) showed that the only significant independent predictor of QoL was disease's activity (B= -22.53, p = 0.001)

Conclusion: Parents correctly report children's QoL in our cohort. QoL was found to be higher in children from Northern Italy and was positively correlated to disease duration and negatively to disease activity, level of fecal inflammation and use of biologics. Disease's activity was the only independent predictor at the multiple regression analysis.

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Modification of intestinal microbiome in children with Crohn’s disease

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Objectives and Study: The etiology of Crohn’s disease (CD) is multifactorial. It seems that both diet and changes of intestinal bacterial flora can play a role in initiating and extinguishing the inflammatory process. The study was aimed at the comparison of intestinal microbiome in patients with CD and health controls as well as the assessment of impact of two forms of therapy used in CD on microbiome. In patients with mild and moderate disease, the effect of exclusive enteral nutrition (EEN) and in patients with severe disease, the influence of therapy with infliximab (IFX) were studied.

Method: 22 children with newly diagnosed CD, 8 pediatric CD patients treated with IFX and 13 controls were enrolled to the study. In patients planned for EEN, stool samples were collected prior to the initiation of treatment (CD-1), during EEN (CD-2) and after the reintroduction of full oral feeding (CD-3). Stool samples from IFX patients were obtained before initiation of therapy (TB-1) and after third dose (TB-2). In healthy children, one stool sample (C) was taken. We conducted metagenomic analysis using Quantitative Insights Into Microbial Ecology (QIIME).

Results: The predominance of Firmicutes bacteria (CD-1: 63.3%, CD-2: 57%, CD-3: 72.8%, TB-1: 57.4%, TB-2: 60%, C: 71.6%) and Actinobacteria (CD-1: 21.9%, CD-2: 35.9%, CD-3: 20.9%, TB-1: 37.39, TB-2: 35.5%, C: 22.9%) was confirmed in all study groups. The amount of Clostridium increased during and after completion of EEN (CD-1: 29.7%, CD-2:39.3%, CD-3: 49%) reaching the level close to that seen in the control group (64.1%). Biological treatment did not influence the amount of Clostridium; it remained on the level of 40.0%, both before as after induction therapy. Both therapeutic modes resulted in the reduction of the amount of Enterococcus bacteria, almost absent in healthy children (respectively, changes for EEN from 14.5% to 5.2%, and for IFX from 4.7% to1.2%). Bacillus population was downregulated in patients on EEN (CD-1: 27.3%, CD-2: 11. 6%, CD-3: 17.3% vs. C: 4.3%). IFX led to the increase of Bifidobacteria (from 8% to 11.3%) but it still remained below the level in health controls (C=16%).

Conclusion: This preliminary results shows that imbalance in intestinal microbiome is present in active CD patients on many taxonomic levels. The patterns of intestinal microbiome changes resulting from the EEN and IFX therapy are different. EEN results in the changes the microbiota profiles in all examined taxonomic levels while IFX exerts impact only on selected taxonomic groups. Therapy focused on restoring natural intestinal flora might be beneficial in patients with Crohn disease.

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Investigation of the long noncoding RNA GAS5 as marker involved in glucocorticoid response in children with inflammatory bowel disease

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Objectives and Study: Despite the introduction of biological therapies, glucocorticoids (GCs) remain widely used for inducing remission in inflammatory bowel disease (IBD), in particular for ulcerative colitis. Given the high incidence of suboptimal response, associated with a significant number of side effects, that are particularly severe in paediatric patients, the identification of subjects that are most likely to respond poorly to GCs is extremely important. In this context, results obtained in our laboratory suggest a role for the long noncoding RNA (lncRNA) growth arrest-specific 5 (GAS5) in modulating GC response. To assess if GAS5 could be considered a marker of GCs resistance we evaluated the association between the lncRNA GAS5 and the efficacy of steroids in IBD paediatric patients, in healthy donors and in vitro models.

Method: For the clinical studies, 19 IBD paediatric patients treated with prednisone 1 to 2 mg/kg/day for 30 days were enrolled at the Paediatric Clinic of IRCCS Burlo Garofolo in Trieste. Peripheral blood was obtained from these patients at diagnosis (T0) and after 4 weeks of treatment (T4). Patients were classified on the basis of their clinical response into 3 groups: steroid resistant (SR), steroid sensitive (SS) and steroid dependent (SD). RNA was extracted from peripheral blood mononuclear cells (PBMCs) and the levels of the lncRNA were quantified.

For the in vitro studies, the effect of methylprednisolone (MP) for 72 h on the proliferation of donors’ PBMCs (obtained from 17 blood donors from the Transfusion Centre, Azienda Ospedaliera Universitaria, Trieste) and human immortalized colon cells LoVo, resistant to GCs, was determined by labelling metabolically active cells with [methyl-3H] thymidine, and the expression of GAS5 was determined by TaqMan Assay. The cytoplasmic or nuclear localization of GAS5 during GC treatment was evaluated by subcellular fractionation and the effect of GAS5 knock-down by transient siRNA transfection on GC sensitivity was also assessed.

Results: Among the 19 patients enrolled, 4 were SR, 8 SD and 7 SS; patients with unfavorable steroid response (SD + SR) presented higher GAS5 levels (Relative Expression= 4.5) in comparison with SS group (Mann-Whitney test P= 0.016), supporting a contribution of GAS5 to steroid ineffectiveness. Donors were divided into 2 groups based on their response to MP and considered good or poor responders if their I250ng/ml values were respectively above or below the median of the whole population. Subjects being poor responders to GCs presented higher levels of GAS5 in comparison with good responders. The correlation between the percentage inhibition of PBMC proliferation and GAS5 expression level was analyzed using the nonparametric correlation coefficient (Spearman rho= -0.73; P= 0.0009).

GAS5 was upregulated in LoVo cells and accumulated more in the cytoplasm in response to MP; in addition, GAS5 knock-down reduced the proliferation during GC treatment.

Conclusion: Our study shows that higher levels of GAS5 can result in the suppression of GC activity. GAS5 could be considered a novel marker useful for the personalization of GC therapy in paediatric IBD patients even though larger studies are needed to confirm these results and to elucidate the molecular pathway that underlines GC resistance.

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**Objectives and Study:** Since 1990s many loci have been associated to inflammatory bowel disease (IBD) trying to shed light on the genetic complexity of this common condition. Despite the undisputable contribution of whole exome sequencing (WES) in identifying rare causative mutations in monogenic forms of IBD, modelling and interpreting polygenic forms of IBD remains challenging. This complex scenario is the result of concurring subtle and common mutations across and within genes on top of an environmental component. For this reason, focusing on a single variant level is not anymore sufficient for explaining the genetic component of this autoimmune disease, but a more comprehensive gene- or pathway-level assessment is needed.

In order to bring clarity and solve such complexity, we present GENEPY, a novel gene-level score for assessing gene disruption level depending on rarity, zygosity and deleteriousness of observed variants on a per-patient basis. To date, few gene-level scores have been developed and none ever being applied to IBD.

**Methods:** Whole exome sequencing data from of 201 paediatric patients affected by IBD and 166 controls was collected and quality controlled. Caucasian individuals were selected for inclusion in the analyses. GENEPY scores were calculated for all ~15 thousand genes over 362 individuals using 16 different deleteriousness scores such as SIFT, CADD, GERP++, Polyphen2, .... Given a specific gene \(g\), the gene score consist can be summarised as following:

\[
S(g) = \sum D \times -\log_{10}(f(a^-) \times f(a^+))
\]

where \(D\) is the deleteriousness score, \(a\) represent any called variants in \(g\) and \(f\) is the frequency of the alleles \(a^-\) and \(a^+\). Variant allelic frequencies were obtained from the 1000 Genomes Project, the ExAc database and ESP6500. The association of \(NOD2\) gene with IBD subtypes was used as benchmark parameter for GENEPY validation. Score performance was verified against SKAT-O test, the current state of the art burden test targeted genomic regions. Differences between IBD and control GENEPY scores were tested using a non parametric two tailed Mann-Whitney U test.

**Results:** GENEPY scores for \(NOD2\) gene identify a statistically significant difference between CD patients (n=122) and controls. P-values were ranging from a maximum of \(9.56 \times 10^{-3}\) using “phastCons” metric to a minimum of \(1.81 \times 10^{-4}\) using “fathamm-MKL” metric with a mean p-value of \(1.83 \times 10^{-3}\) . GENEPY-based p-values were one order of magnitude more significant compared to a SKAT-O association test (\(p = 3.0 \times 10^{-2}\) ). Moreover, SKAT-O test on \(NOD2\) was also performed considering only rare variants (MAF<0.05) and no improvement were observed.

**Conclusions:** In this work we provide a novel patient-specific gene-based score capable of modelling the combined effect of multiple variants depending on their rarity, zygosity and predicted pathogenicity. GENEPY score was successfully validated against SKAT-O test, providing a higher level of statistical significance and no spurious associations. Moreover, the continuous nature of the GENEPY scores, makes this system suitable for a large variety of downstream analyses, with a particular accent on machine learning applications.

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Prognostic factors for colectomy and acute severe colitis in paediatric ulcerative colitis: A systematic review

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³Erasmus MC - Sophia Children's Hospital, Rotterdam, Netherlands

Objectives and Study: Identifying variables predictive of outcomes in ulcerative colitis (UC) is important for guiding risk stratification and tailoring treatment protocols. Children present a unique treatment challenge due to longer life expectancy and a more aggressive disease course than in adults. We thus undertook a systematic review of the evidence relating to prognostic factors for disease outcomes in paediatric UC.

Method: A systematic review of Pubmed and EMBASE was conducted in June 2017. English language observational or controlled studies published from 1992 regarding patient and disease characteristics associated with surgery, disease activity, and complications in children (0-18) with UC were eligible for inclusion. Abstracts were screened independently by one of three reviewers; selected studies were assessed by two reviewers, while the third resolved conflicting decisions. Risk of bias was assessed using the Ottawa Newcastle scale.

Results: 10,767 studies were screened, of which 522 full-text-manuscripts were assessed, and 60 were included (all observational). 39 discussed associations with colectomy, 4 acute severe colitis (ASC), and 18 other disease related outcomes. Male gender (in 4 studies including 999 patients, HR 1.17-4.16), weight loss at diagnosis (HR 2.55-4.01), upper-GI involvement, extraintestinal manifestations (HR 2.03-3.40), and PUCAI at diagnosis (HR 1.07-3.63) and 3 months thereafter (OR 4.47) were associated with increased risk of colectomy. Smoking (aHR 0.23) as well as PSC (OR 0.21), may be protective in children. Age at diagnosis, race, family history of IBD, symptom duration prior to diagnosis, genetic polymorphisms, serology, endoscopic severity and any blood test at diagnosis were not consistently associated with colectomy. Studies exploring the predictive value of disease extent and disease extension showed conflicting results. Limited data suggest that disease-severity at onset, measured by PUCAI or endoscopy, and albumin level may predict development of ASC, whereas other blood tests, age, and disease extent do not. Table 1 lists factors for which at least one study reported an association with the outcome of interest (number of studies which demonstrated a significant (+) association, amongst all studies examining the predictor, is shown in brackets).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Demographic associations</th>
<th>Phenotypic associations</th>
<th>Serologic and genetic predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy</td>
<td>Age (2/17+) Male gender (4/13 +) Weight loss (1/1+) Smoking (protective, 1/1+)</td>
<td>PUCAI diagnosis (3/5+) PUCAI 3 months (1/2+) Lab values? (5/8+ for inconsistent markers) Disease extent (4/10+) Disease extension (1/3+) Upper GI disease (1/1+) EIM (2/3+) PSC (protective, 1/2+, 1 trend) IBDU (protective, 1/1+)</td>
<td>Genetic polymorphisms (1/6+), pANCA+/ASCA-status ? (1/1+)</td>
</tr>
<tr>
<td>Development of ASC</td>
<td>Age at diagnosis (0/2+)</td>
<td>Endoscopic severity (1/1+) PUCAI (diagnosis/3months) (1/1+) Albumin (1/1+)</td>
<td></td>
</tr>
</tbody>
</table>

[Table 1]
Conclusion: Contrary to adult data, age at diagnosis does not predict colectomy or severity of disease course in paediatric UC. We identified several factors which may be associated with complicated disease course and help guide treatment algorithms.

Note: This abstract has been developed subsequent to an AbbVie sponsored literature review of complicated outcomes in UC however, AbbVie was not involved in the development of the abstract. AbbVie selected the discussion participants and reviewed the draft for scientific accuracy, but the authors determined the final content.
Utility of anti-TNF therapeutic drug monitoring in IBD: A systematic review and meta-analysis

Amanda Ricciuto¹, Jasbir Dhaliwal¹, Thomas D. Walters¹, Anne M. Griffiths¹, Peter C. Church¹

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Objectives and Study: Much of the evidence supporting the use of therapeutic drug monitoring (TDM) to guide anti-TNF therapy in IBD derives from cross-sectional studies showing associations between various endpoints and drug trough levels. However, the direct evidence comparing outcomes with and without TDM is less clear. We performed a systematic review to evaluate the efficacy of TDM for optimising outcomes in anti-TNF-treated IBD patients.

Method: We searched MEDLINE, Epub Ahead of Print, EMBASE and Cochrane from inception to March 2017 for randomized (RCTs) and observational studies comparing reactive and proactive TDM to each other or(empiric anti-TNF optimization in IBD. The primary outcome was clinical remission. Secondary outcomes were clinical response and relapse, drug discontinuation, anti-drug antibodies (ADAs), endoscopic healing, costs and adverse events. Pooled odds ratios (ORs) were calculated using a random-effects model. Risk of bias was assessed with the Cochrane risk of bias and Newcastle-Ottawa tools.

Results: The search identified 9 studies (3 RCTs (1 low, 1 unclear and 1 high risk of bias); 6 observational studies (all high risk of bias); 4 studies available as abstracts). Two RCTs and 2 cohort studies compared proactive TDM and empiric care; 1 RCT and 2 cohort studies compared reactive TDM and empiric care; and 2 cohort studies compared proactive and reactive TDM. All studies primarily examined IFX maintenance, in adults. TDM was not associated with superior clinical remission rates in any of the studies (Table 1). Benefits were seen for other outcomes, however, particularly those pertaining to durability of drug response. Patients receiving proactive TDM (vs empiric optimization) were significantly less likely to relapse over 1 year (OR 0.37, 95% CI: 0.16-0.84) in an RCT, and had significantly longer time to relapse in a retrospective study. Over 2 to 5 years, proactive TDM was associated with significantly lower anti-TNF discontinuation rates compared to empiric care in a retrospective study (OR 0.19, 95% CI 0.05-0.65), and compared to reactive TDM in a pooled analysis of two retrospective studies (OR 0.12, 95% CI 0.05-0.27). ADA development was less frequent with reactive TDM vs empiric care in a retrospective study, and with proactive vs reactive TDM in another retrospective study (OR 0.24, 95% CI 0.05-0.82). The 3 studies to examine cost found cost reductions with TDM (mean difference -$7,006, 95% CI -$12,848 to -$874 per patient per year with reactive TDM in an RCT). A small number of retrospective studies suggested benefit for surgery and endoscopic healing, but findings were conflicting and the one RCT to evaluate endoscopic outcomes found no difference. TDM was not associated with increased adverse events.

Conclusion: The direct evidence supporting the use of TDM to improve outcomes in IBD is relatively scarce and conflicting. The existing evidence does not support the use of TDM to maintain clinical remission. Several studies do, however, fairly consistently suggest a benefit in terms of durability of drug response, primarily with proactive TDM. Reactive TDM has been associated with cost savings. The above pertains solely to IFX maintenance therapy in adults; little is known about the efficacy of TDM for induction, non-IFX anti-TNF agents, and children.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proactive TDM vs empiric studies</th>
<th>Proactive TDM vs empiric OR or mean difference (95% CI)</th>
<th>Reactive TDM vs empiric studies</th>
<th>Reactive TDM vs empiric OR or mean difference (95% CI)</th>
<th>Proactive vs reactive TDM studies</th>
<th>Proactive vs reactive TDM OR or mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>2 RCT (n=373); 1 observational</td>
<td>0.85 (0.50-1.44) pooled RCT; 0.82 (0.44-1.52) observational</td>
<td>1 RCT (n=69); 1 observational</td>
<td>1.89 (0.72-4.92) RCT; 1.17 (0.75-1.82) observational</td>
<td>0 studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical response</td>
<td>1 observational (n=80)</td>
<td>26.9 (1.48-490)</td>
<td>1 RCT (n=69); 2 observational</td>
<td>2.50 (0.89-7.02) RCT; 1.32 (0.75-2.34) pooled observational</td>
<td>0 studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>1 RCT (n=251); 1 observational</td>
<td>0.37 (0.16-0.84) RCT; 0.65 (0.33-1.30) observational</td>
<td>0 studies</td>
<td>N/A</td>
<td>0 studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>1 RCT follow-up study (n=215); 1</td>
<td>0.18 (0.03-0.93) RCT; 0.19 (0.05-0.65) observational</td>
<td>1 RCT (n=69); 2 observational</td>
<td>1.18 (0.72-1.96)</td>
<td>2 observational (n=390)</td>
<td>0.12 (0.05-0.27) pooled</td>
</tr>
<tr>
<td>Antidrug antibodies</td>
<td>1 RCT (n=251)</td>
<td>0.13 (0.01-2.62)</td>
<td>0 studies</td>
<td>N/A</td>
<td>1 observational (n=264)</td>
<td>0.24 (0.12-0.50)</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>1 RCT (n=122)</td>
<td>0.95 (0.45-2.02)</td>
<td>1 observational (n=312)</td>
<td>2.21 (1.40-3.50)</td>
<td>0 studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Surgery</td>
<td>1 observational (n=218)</td>
<td>1.78 (0.52-6.10)</td>
<td>1 observational (n=312)</td>
<td>0.53 (0.29-0.98)</td>
<td>1 observational (n=264)</td>
<td>0.29 (0.12-0.66)</td>
</tr>
<tr>
<td>IBD-related medical costs</td>
<td>1 RCT (n=251)</td>
<td>-€300</td>
<td>1 RCT (n=69)</td>
<td>-$7006 (-12848 to -874)</td>
<td>0 studies</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1. Study outcomes

Disclosure of interest: A. Ricciuto has received speaker fees from AbbVie and research fellowship support from Janssen; T.D Walters speaker fees from Janssen and Nestle, consultancy fees from Janssen and Ferring, and research support from Janssen; A.M. Griffiths speaker fees and consultancy fees from Janssen and Abbvie, consultancy fees from Pfizer, Takeda, Gilead and Ferring, and research grants from AbbVie; Peter C. Church consultancy fees from AbbVie, Ferring and Janssen, and research support from Abbvie.

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Infliximab trough levels are predictive for infliximab efficacy in paediatric patients with inflammatory bowel disease on maintenance therapy

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Objectives and Study: The role of therapeutic drug monitoring during maintenance treatment in paediatric inflammatory bowel disease (IBD) is poorly studied. The aim was to determine whether infliximab (IFX) trough levels (TL) correlate with long-term remission in children receiving maintenance IFX.

Method: In this cross-sectional study all children with Crohn's disease (CD) or ulcerative colitis (UC) receiving maintenance IFX at our referral centre were included. All children received proactive drug monitoring with the therapeutic window defined between 3-7 µg/mL (conform adult studies). IFX TL were analysed using the Ridascreen IFX Monitoring ELISA. Demographics, disease activity indices, biochemical values and endoscopic reports were recorded retrospectively. Clinical remission was defined as PUCAI/PCDAI < 10 and biochemical remission as CRP ≤5 mg/L and ESR ≤ 20 mm/h. Patients were considered in deep remission if both criteria (clinical + biochemical remission) were met. Endoscopic remission was defined as absence of ulceration. Mann-Whitney U-test was used to compare responders from poor-responders and correlations were analysed with Spearman's rho. All data are presented as median [IQR] and alpha was set at 0.05.

Results: A total of 45 patients (30 CD and 15 UC; 47% male; median age of 15.4 years [12.2-16.6]) and 617 IFX TLs (median 10 per patient [5.5-21]) were included. Median age at start of IFX was 12.8 years [9.6-15] with a median disease duration prior to starting IFX of 5.0 months [2.0-9.5]. Mean administered IFX dose was 6.8 mg/kg [5-10] and the mean maintenance interval 5.6 weeks [4-6]. At start of maintenance 76% was on concomitant immunosuppressants. Median IFX TL during maintenance were significantly higher in children who were in clinical remission (5.4µg/mL [3.8-8.1] vs 4.1µg/mL [2.6-6.7], p=0.0001), biochemical remission (5.2µg/mL [3.7-7.7] vs 4.2µg/mL [2.5-6.6], p=0.0001), deep remission (5.7µg/mL [3.9-8.4] vs 4.2µg/mL [2.6-6.7], p=0.0001) and endoscopic remission (6.2µg/mL [3.9-9.5] vs 3.2µg/mL [2.3-5.7], p=0.005; see figure). With a median follow-up of 24 months [10-40] under IFX, 36/45 (80%) patients were in clinical and 27/37 (73%) patients in endoscopic remission at last follow up. IFX TL correlated significantly with CRP, ESR, albumin and PUCAI/PCDAI (all ps<0.005).

Conclusion: In this paediatric IBD cohort treated with IFX maintenance, children who demonstrated clinical and/or endoscopic remission had significantly higher IFX TL. Our data support the value of proactive drug monitoring in children to improve long-term outcome. Whether the same therapeutic window as in adults needs to be pursued in children, needs to be investigated in prospective studies.
Disclosure of interest: I. Hoffman: Nutrica, nestlé, Mead Johnson, Abbvie; A. Gils: MSD, Janssen
Biologics, Pfizer, Takeda, Abbvie, R-biopharm, apDia, Merck; M. Ferrante: Takeda; Abbvie,
Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, MSD, Pfizer; Chiesi, Tillotts, Zeria; S.
Vermeire: Takeda, MSD, Abbvie, Pfizer; Ferring, Shire, Janssen, Pfizer Inc, Galapagos,
Genentech/Roche, Celgene, Mundipharma, Eli Lilly, SecondGenome, GSK; Dr. Falk Pharma, Hospira,
Pfizer Inc and Tillotts

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Impact of Exclusive Enteral Nutrition as primary treatment on adipokines concentration in children with newly diagnosed Crohn Disease

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Objectives and Study: Crohn’s disease (CD) is characterized by imbalance between innate and adaptive immunologic response and proinflammatory cytokines dominance. Hypertrophy of mesentric adipose tissue, surrounding the inflamed bowel and local alteration in the production of both pro- and anti-inflammatory adipokines indicates visceral fat contributions in chronic inflammation present in CD. The aim of the study was to assess changes in five adipokines (adiponectin, chemerin, leptin, resistin and visfatin) concentrations in children with newly diagnosed CD prior to diagnosis and after gaining remission on 6-weeks course of Exclusive Enteral Nutrition (EEN).

Method: 45 children (aged 7-17) with newly diagnosed mild or moderate Crohn’s disease (Paediatric Crohn’s Disease Activity Index - PCDAI & LT; 40 points), with disease location: L1, L2, L3 and disease phenotype: B1 according to the Paris classification, qualified to EEN induction remission treatment, were enrolled in to the study. 23 children without any gastroenterological disorders, served as controls. Standard laboratory tests, faecal calprotectin in stool and adipokines concentration: adiponectin, chemerin, leptin, resistin and visfatin were measured twice in studied group (before and after 6 weeks period of EEN) and once in controls.

Results: 36 children (80%) gained remission after 6-weeks course of EEN (PCDAI & LT: 10), 24 children (53%) reached normal CRP level and 9 (20%) reached remission with normal CRP level and calprotectin. On diagnosis chemerin and resistin concentrations were significantly higher in CD compared to controls (256.7 ± 95 vs 153.3 ± 86.7; p<0.005) and (8.42 ± vs 5.09 ±; p<0.005) respectively. After 6-weeks course of the EEN concentrations of both chemerin and resistin decreased after treatment (243 ± 86.7 and 4.69 ± 1.62). Baseline visfatin and adiponectin concentrations were significantly higher in CD, but show no statistical significance (2.09 ± 1.35 vs 1.66 ± 0.95 and 14470.2 ± 6312.8 vs 10721.6 ± 5955.6). Treatment induced further increase in adiponectin concentrations (16765.6 ± 9203.1) and decrease in visfatin concentrations (1.92 ± 1.28). Baseline leptin concentrations were significantly decreased in CD compared to controls (7.15 ± 10.2 vs 12.48 ± 10.3; p<0.005) and significantly increased after treatment (13.42 ± 13.2; p<0.05).

Conclusion: Visceral fat in CD modulates serum adipokine levels by increasing chemerin, resistin, adiponectin, visfatin concentrations and by suppressing leptin production. It is possible that EEN influence on disease activity and inflammatory markers by decreasing elevated concentrations of chemerin, resistin, visfatin and increasing adiponectin and leptin concentrations.

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Prospective evaluation of the microbiome in the pouch and ileum in patients who had a J-pouch with ileo-anal anastomosis

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Objectives and Study: Previous studies of fecal samples obtained from the ileal pouch have suggested that decreases in microbial diversity and protective bacteria along with increases in inflammatory bacteria may predispose to pouchitis. The aim of this study was to evaluate the mucosal associated microbiome in the pouch, ileum proximal to the pouch, and stool.

Methods: Twenty-one patients less than 21 years of age had colectomy for ulcerative colitis (UC). All samples from the pouch were collected from subjects undergoing pouchoscopy, who provided informed consent and did not have a bowel lavage prior to the procedure. Pouch biopsies from an adjacent location were obtained both before and after washing with a jet of water. Additional biopsies were obtained from the ileum proximal to the pouch. Biopsies from each area were sent to pathology for routine histological examination. Stool from the unprepared pouch was collected. All samples were immediately snap-frozen in liquid N₂ or dry ice. Amplicons of the V4 region of 16s rRNA were sequenced on an Illumina MiSeq platform. Sequences were joined, denoised, filtered for chimeras, and clustered into OTUs (at 97% similarity) using the QIIME pipeline. OTUs were classified against the GreenGenes database. Statistical analysis was performed using the scikit-learn library and Python scripts. Biopsies from the rectum and ileum of children with treatment-naïve UC were similarly processed and served as a comparison group. Twelve pouch patients had samples from one procedure; whereas, 9 patients had samples from 2-5 procedures.

Results: Washing the mucosa did not affect the composition of the mucosa-associated microbiome. The composition of the microbiome in the ileum of treatment naive children with UC differs from the microbiome in the rectum (Figure 1A). The microbiome in the ileum proximal to the J-pouch is similar to the microbiome in the pouch (Figure 1B). The severity of inflammation in the pouch appears to have little impact on the composition of the microbiome (Figure 1C and 1D).
Conclusion: Washing the mucosa minimally alters the mucosal microbiome. Unlike the ileum and the rectum in patients with an intact colon, the microbiome in the J-pouch is closer in composition to the ileum. The severity of pouchitis does not appear to substantially alter the microbiome composition which appears to be relatively stable over time. We speculate that the development of pouchitis might be related more to the number of bacteria in the pouch rather than the composition of the microbiome.

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Features of the gut microbiome in very early onset inflammatory bowel disease with interleukin10 receptor deficiency

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Objectives and Study: We are aimed to characterize the microbiome dysbiosis in children with interleukin10 receptor(IL10R)-deficiency who developed inflammatory bowel disease(IBD) at a very young age.

Method: We collected faecal samples from patients with identified mutations in IL10R and age-matched healthy controls. Microbial DNA was extracted from the faecal samples. And all diversity analysis was based on the 16S ribosomal RNA gene sequencing data.

Results: We enrolled sixteen very early onset IBD patients (VEOIBD) confirmed with IL10R deficiency and sixteen age-matched controls. We observed significantly reduced community diversity and evenness index in VEOIBD. Venn diagram shows VEOIBD and healthy controls shared 135 genera. Specifically, Lachnospiraceae_ND3007_group, Megasphaera, and Anaeroglobus were absent in VEOIBD. In contrast, there are 102 genera only present in VEOIBD group, such as Faecalitalea, Akkermansia and Peptoniphilus. Principal component analysis performed on operational taxonomic units(OTU) level shows a greater dispersion within the VEOIBD group. So, we compared the microbial composition of the 16 pairs of VEOIBD and age-matched control. In genus-level measurements, we found that a single genus is often dominant in VEOIBD. For example, the relative abundance of the Klebsiella was 99.38% and 97.57% in two VEOIBD patients, respectively. In addition, Escherichia-Shigella (relative abundance 97.29%), Enterobacter (relative abundance 96.51%), and Enterococcus (relative abundance 92.52%) seemingly contributed to the dysbiosis.

Conclusion: Gut Microbiome in VEOIBD with IL10R deficiency is associated with a reduction of microbial diversity. This study revealed that higher variations in microbial compositions existed among VEOIBD patients than among controls.

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**The study of NLRP3 inflammatory signal pathway in helicobacter pylori-associated immune thrombocytopenia**

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**Objectives and Study:** There is a high prevalence of helicobacter pylori (*H. pylori*) in the world, and more than 50% of the population has *H. pylori* infection. *H. pylori* is not only related to gastrointestinal diseases such as chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma. It is also associated with diseases outside the gastrointestinal tract such as hematological disorders, including immune thrombocytopenia (ITP). But the mechanism of how *H. pylori* participates in ITP is not fully elucidated. It has been reported that *H. pylori*-induced ITP may be related to genetic factors, immune factors and inflammatory factors and so on. The activation of the NLRP3 inflammasome signaling pathway plays an important role in many autoimmune and autoinflammatory diseases, including ITP. In our study, we examined the protein expression level of NLRP3 and caspase-1 in the peripheral blood mononuclear cells (PBMCs) of each group, and clarified the role and mechanism of NLRP3 signaling pathway induced by Helicobacter pylori (*H. pylori*) in idiopathic thrombocytopenia (ITP).

**Method:** Collected the anticoagulant fresh blood of the health children and the children with ITP combined with *H. pylori* infection and ITP who were first diagnosed, and *H. pylori* infection in our hospital from October 2016 to August 2017. The protein expression levels of NLRP3 and Caspase-1 in PBMCs were detected by western blotting.

**Results:** There were 118 cases, 69 males (58.5%) and 49 females (41.5%). There were 29 cases (24.6%) of ITP with *H. pylori* infection, 30 cases (25.4%) of ITP, 29 cases (24.6%) of *H. pylori* infection, and 30 cases (25.4%) of healthy controls. The mean ages were 6.86, 6.81, 7.17 and 5.57 years old, respectively. There were no significant differences in age, gender and the platelet count at the time of starting of the investigated treatment (P>0.05). Our results showed significantly higher protein expression levels of NLRP3 and Caspase-1 in patients with ITP combined with *H. pylori* infection and Caspase-1 in patients with ITP combined with *H. pylori* infection than in healthy controls. Twenty three cases (79%) of ITP combined with *H. pylori* infection experienced anti-*H. pylori* treatment, of which 16 cases (69.5%) of children after treatment review *H. pylori* turned negative. Eight (50%) of the 16 patients achieved a significant therapeutic effect and the symptoms were completely relieved, 3 cases (19%) markedly effective, 5 cases (31%) ineffective. The protein expression of NLRP3 and Caspase-1 was lower than before treatment (P < 0.05), but still higher than that in the healthy control group (P < 0.05). The average of the platelet counts at the time of starting of the investigated treatment of the three groups was (22.38±11.17)×10⁹/L (completely relieved), (9.33±2.88)×10⁹/L (effective), and (10.80±7.75)×10⁹/L (ineffective) respectively, and no significant differences were observed (P > 0.05).

**Conclusion:** *H. pylori* infection can activates the NLRP3 inflammatory complex signaling pathway; ITP may be associated with activation of NLRP3 inflammatory signaling pathway; After *H. pylori* infection, ITP may be induced by activating the NLRP3 inflammatory signaling pathway.

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Efficacy of the invasive diagnostic tests in symptomatic Helicobacter pylori infected children: a single center study

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Introduction: *H pylori* is usually acquired mostly in childhood and leads to prolonged exposure to this potentially carcinogenic agent. There is a genetic variation of the main molecular virulence factors among different geographic regions that affects clinical evolution.

Aim: The aim of this study was to evaluate the accuracy of invasive diagnostic tests for *H pylori* infection in symptomatic infected children who were referred for endoscopic evaluation and to analyze the prevalence of selected virulence genes (*cag A, vac A, ice A*).

Patients and methods: We conducted a prospective study of 300 consecutive symptomatic children (age range 1-18 years) with uninvestigated dyspepsia and extradigestive signs suggestive for an organic disease requiring a first upper gastrointestinal endoscopy. The gastric biopsy specimens were evaluated by rapid urease test, histological examination, culture and polymerase chain reaction (PCR). A positive *H pylori* status was defined by at least two standard invasive different tests.

The *vac A* and *ice A1* genes were identified by multiplex PCR, whereas the *cag A* and *ice A2* genes were detected by PCR. The sensitivity, specificity, predictive positive value (PPV) of the invasive tests used, was evaluated. Statistical analysis were performed using the Graph Pad Prism Program. A p-value less than 0.05 was considered as statistically significant.

Results: Active *H pylori* infection was documented in 145 of the 300 studied children (48.33%). Endoscopic nodular gastritis was identified in most of the cases (105/145 patients; 72.41%). The rapid urease test was positive in 115 children (sensitivity 85.19%, specificity 93.94%, PPV 92%) and histopathology in 129 cases, with a higher sensitivity (89.58%) and VPP (99.23%). Culture was performed in 108 cases, with the lowest sensitivity results (74.48%) but with higher specificity (100%) and VPP (100%). There was no difference in specificity and PPV between histology and culture, as opposed to RUT, in which case they were lower.

*H pylori* infection virulence genotype was analyzed by conventional PCR which was positive 140/145 infected children with higher levels of specificity (100%) and VPP (100%), which were significantly higher compared to other invasive tests used in this study. The *cag A* gene was detected in 96 of 140 studied cases (68.57%), compared with *vac A* gene which was identified in all 140 cases isolated by PCR, with the predominant *vacA* s1/m1 genotype (86/140 cases; 61.42%), which ensures an intense cytotoxic activity associated to a high risk of ulcer and gastric cancer, followed by *vacAs1m2* (36.42%) and *vacAs2m2* (22.75%) with lowest pathogenicity. *H pylori* strains positive for *ice A1* gene were identified in 100/140 cases (71.42%), which were associated with the most virulent genotypes (*vac A* s1/m1 and *vac A* s1/m2). The most virulent genotype *cag A/vac A* s1m1 of *H pylori* strains were associated with higher bacterial densities (p&LT; 0.001) and with non-atrophic antral gastritis and antral nodularity (p&LT; 0.001).

Conclusions: Our data suggest that among invasive test PCR had a significantly higher sensitivity, specificity (p &LT; 0.001) compared with other invasive tests. There was no difference in specificity and PPV between histology and culture, as opposed to RUT, in which case they were lower.

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Targeting Wnt/β-catenin signaling in pediatric familial adenomatous polyposis patient derived cell lines by γ-Mangostin, a natural xanthone derivative

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Objectives and Study: Familial adenomatous polyposis (FAP) is an autosomal inherited predisposition to colorectal adenomatous polyps, intestinal and extra-intestinal malignancy starting from childhood. FAP is caused by germline mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q22, resulting in aberrant Wnt/β-catenin signaling. FAP has a nearly 100% lifetime risk of colon cancer by the age of forty and prophylactic total colectomy is required during the teenage years or early adulthood. There is continued interest in chemo preventive strategies to delay or mitigate the need for colectomy, including the use of novel compounds derived from medicinal plants. γ-Mangostin is a major bioactive compound present in Mangosteen fruit from Garcinia mangostana, which possess significant anti-cancer activity. The aim of the study is to determine the effects of γ-Mangostin against FAP patient derived cell lines and determine if the mechanism involves suppressing Wnt/β-catenin signaling.

Methods: The study was presented and approved by the institutional (CMH) ethical conduct of research review committee. Pediatric (< 21 year) FAP patients undergoing standard of care surveillance colonoscopy underwent additional, healthy colonic epithelial biopsies from which were derived viable cells using specific media. Cell proliferation were assessed by hexosaminidase and clonogenicity assays. Cell cycle was analyzed by FACS analysis using propidium iodide staining. Apoptotic proteins were measured by western blot analysis. The growth of spheroids was also evaluated. In addition, Wnt signaling proteins were measured by western blot analysis and immunofluorescence analysis. Further, proteosomal degradation of β-catenin was assessed by employing MG132 treatment.

Results: γ-Mangostin inhibits proliferation and colony formation in a dose and time dependent manner in the FAP patient derived cell lines. In addition, γ-Mangostin induces S-phase and G2/M arrest, thereby reducing cyclin D1 levels. Furthermore, it inhibits the expression of anti-apoptotic protein Bcl2. γ-Mangostin significantly inhibits spheroid formation suggesting that it affects stem cells. Moreover, γ-Mangostin treatment decreased the expression of Wnt signaling proteins and its downstream targets such as cyclin D1 and c-Myc, which suggest that it inhibits the adenoma growth through Wnt/β-catenin signaling pathway. In addition, MG132 treatment inhibited γ-Mangostin induced degradation of β-catenin suggesting the involvement of proteosomal degradation pathway.

Conclusion: Cumulatively, this data suggest that γ-Mangostin inhibits FAP patient derived cells growth through Wnt/β-catenin signaling pathway. γ-Mangostin may be a promising therapeutic agent for Familial Adenomatous Polyposis.

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Ideal diagnosis and management of children with Blue Rubber Bleb Nevus Syndrome from a multi-centric series

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Objectives of the study: To present and analyze a case series of paediatric patients with Blue Rubber Bleb Naevus Syndrome (BRBNS) and to describe diagnostic approaches and management options applied.

Methods: Multi-centric, retrospective study, evaluating diagnosis and management of paediatric patients aged 0-18 yrs with BRBNS.

Results: Seventeen patients (12 male) diagnosed with BRBNS were included. Age at first presentation was birth to 12 years old (median 2.8 years) with follow-up of 1-18 years (median 9.5 years). Cutaneous venous malformations were present in 13 patients (76%) and gastrointestinal venous malformations in 15 (88%). Lesions were also found in other organs such as muscles, joints, central nervous system, eyes, parotid gland, spine, kidneys and lungs. Gastrointestinal lesions were more common in the small intestine (14) than in the stomach (8) and colon (8). Significant variations among centres were recorded in management. Endoscopic therapy and surgical therapy alone failed to prevent recurrence in 89% and 70% respectively. A good surgical response was observed in post-pubertal patients. In younger children and in patients with muscle-skeletal or other organ involvement, medical treatment was more frequently employed with sirolimus being the most effective, with 100% success rate (5 patients treated) in our series - although poor compliance with sirolimus and subtherapeutic ranges led to recurrence in a minority.

Conclusions: Considering the wide expression of BRBNS lesions with frequent multi-organ involvement, diagnosis and management of the patients should be multidisciplinary. Treatment includes conservative, endoscopic, surgical and medical options. This analysis represents the world experience in children to date.

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A Cochrane systematic review of prophylactic probiotics in infantile colic

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Objectives and Study: Infantile colic is defined as periods of inconsolable, unexplained, and incessant crying in a seemingly healthy infant. There is growing evidence to suggest that intestinal flora in colicky infants differ from normal individuals, and it is suggested that probiotics can redress this balance and provide a healthier intestinal microbiota landscape. Previous reviews have investigated the use of probiotics to treat established colic, but we set out to systematically review the evidence for the use of probiotics to prevent the onset of infantile colic.

Methods: The Cochrane Central Register of Controlled Trials, MEDLINE and trial registers were searched (Inception - July 2016). Manufacturers of probiotics were contacted to identify unpublished trials. References of trials were also searched. Abstracts were considered for inclusion if full details to judge inclusion were offered or available from the authors. Data extraction and assessment of methodological quality of included studies were independently performed by two authors. Analysis was completed in accordance with the intention to treat approach.

Results: The search yielded 2369 results, and of these, 24 studies were selected for full text review. Six published studies (n=1886) met the inclusion criteria. Two studied lactobacillus reuteri DSM, two multi-strain probiotics, one lactobacillus rhamnosus, and one lactobacillus paracasei and bigidobacterium animalis. The risk of bias was low for randomisation for all six trials. Allocation concealment was low in two studies and unclear in others. All studies were blinded and bias was low for incomplete outcome data and selective reporting in all. Meta-analysis of three studies (n=1148) found no statistically significant difference in primary occurrence of colic. However, sensitivity analysis using a fixed effects model showed a statistically significant difference favouring probiotics (RR 0.58, 95% CI 0.38-0.90). An analysis of the crying time in term babies (minutes per day) at study end showed a significant mean difference of -20.65 (95% CI -47.23 to -5.92). Subgroup analysis of the most studies agent (L Reuteri) was also significant with a reduction in daily crying of 44 minutes (95% CI -66.6 to -21.9). Meta-analysis of all six studies (n=1851) showed no difference in adverse events (RR1.02, 95% CI 0.14-7.21).

Conclusions: Although the meta-analysis showed no difference in the use of probiotics on primary outcome analysis, our wider analysis suggests efficacy of probiotics for infantile colic with reduced occurrence of colic and reduced crying time. There is no difference in adverse events, suggesting safety. As this indication is that such supplementation is safe and probiotics are freely available in many countries to parents, rather than through paediatricians exclusively, future research is key in this context.

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Sustained remission of eosinophilic esophagitis after discontinuation of dietary elimination in children

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Objectives and Study: Eosinophilic Esophagitis (EoE) is a chronic immune/allergen mediated inflammatory disease characterized by both esophageal dysfunction and eosinophilic infiltration of the esophageal epithelium. Current treatments include elimination diets and topical steroids. Symptoms and/or eosinophilic infiltrates generally recur following withdrawal of treatment. The aim of this study was to describe a subset of children with EoE brought into remission with elimination diets, who remained in both clinical and histological remission (<15 Eos/hpf) despite complete reintroduction of all eliminated food allergens, and to assess for factors that could differentiate them from other EoE patients.

Methods: A retrospective chart review of pediatric patients diagnosed with EoE and included in the retrospective pediatric eosinophilic esophagitis registry (RetroPEER) was performed. Patients treated with elimination diets who remained in both clinical and histological remission despite full antigenic reintroduction were identified, and records were re-evaluated for accuracy of data. We compared these patients to the entire EoE cohort, and to EoE patients treated solely with elimination diets.

Results: Of 410 pediatric EoE patients from 25 European centers, 15 (3.7% of the whole cohort, 10.6% of those treated only with diet) remained in sustained clinical and histological remission following complete allergen reintroduction. The median time from the final reintroduction to the most recent endoscopy was 15 weeks (IQR 8-68). Neither male gender (73.3% vs 77.4%), age at diagnosis (8.4±4.7yrs vs 8.9±4.8yrs), performance of a PPI test (86.7% vs 69.7%), personal (69% vs 67%) or family history (53.8% vs 60.6%) of atopy could differentiate patients with resolving disease from other patients (p>0.15 for all comparisons). Of presenting symptoms, only failure to thrive/poor weight gain was significantly more frequent in patients with resolved disease (26.7% vs. 9.9%, p=0.037).

Conclusions: Sustained remission of EoE in children treated with elimination diets is feasible although uncommon. None of the examined parameters differentiate resolving vs. non-resolving EoE. Reintroduction of triggering foods may be considered periodically to assess the need for continuous allergen elimination in children with EoE.

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Immune function and infectious complications in children with multiple intestinal atresia

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Objectives and Study: Prior case reports have described an association between multiple intestinal atresia (MIA) and combined immunodeficiency. Children with MIA and immune deficiency have been reported to have worse outcome, with significant risk for graft-versus-host disease following small bowel transplantation. This study aimed to investigate the immune function and its impact on the patient outcome in children with MIA, compared to those with isolated intestinal atresia (IIA).

Methods: This was a retrospective chart review of children aged 0-19 years, who had been evaluated for intestinal atresia at our institution from January 2000 to December 2016. Patients were identified from electronic medical records based on ICD-9 code. Data were collected for patient characteristics, comorbidities, history of transplant, immunologic work-up, infection-related hospitalizations, including hospitalizations for bacteremia/sepsis, pneumonia, acute gastroenteritis, and urinary tract infection. Groups of children with MIA and IIA were compared using chi square test or Fisher’s exact test for categorical variables, and using t-test for continuous variables.

Results: Among 59 patients with intestinal atresia identified during the study period, 54 children (22 with MIA) were eligible for data analysis. Patient characteristics and immunologic evaluation between the two groups are summarized in the table. The median patient’s age at evaluation was 0.4 years (interquartile range [IQR]=3.5). The median follow-up was 6.1 years (IQR=2.4). Three children (2 MIA and 1 IIA) underwent liver-small bowel transplant, and one IIA patient received isolated liver transplant. The median neutrophil count was significantly lower in MIA patients, 3650 (IQR=1918) versus 5000 (IQR=7600) in IIA patients (p=0.005). Immunoglobulin (Ig) levels were available in 14 MIA patients, and the median IgG level, 396 mg/dl (IQR=305), was lower than the normal range. Regarding infectious complications, children with MIA had higher rate of frequent bacteremia (defined as greater than 3 episodes), 66.7% versus 20.0% in the IIA group (p=0.13). Patients with MIA also had higher rate of infectious complications requiring hospitalization, 77.8% compared to 41.2 % in those with IIA (p=0.11).

<table>
<thead>
<tr>
<th></th>
<th>Multiple intestinal atresia (n=22)</th>
<th>Isolated intestinal atresia (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>0.5 (4.2)</td>
<td>0.3 (3.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (45.5)</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Hispanic/Others</td>
<td>11 (50.0)/6 (27.3)/5 (22.7)</td>
<td>17 (53.1)/4 (12.5)/11 (34.4)</td>
</tr>
<tr>
<td>Neutrophil count* (/mm3), median (IQR)</td>
<td>3650 (1918)</td>
<td>5000 (7600)</td>
</tr>
<tr>
<td>Lymphocyte count (/mm3), median (IQR)</td>
<td>4250 (4775)</td>
<td>4400 (2400)</td>
</tr>
<tr>
<td>Immunoglobulin (mg/dL), median (IQR) IgG/IgM/IgA</td>
<td>396 (305)/53 (31)/31 (59)</td>
<td>417/126/16 (available only in 1 patient)</td>
</tr>
</tbody>
</table>

*p-value = 0.005

[Patient characteristics and immunologic evaluation]

Conclusion: Children with MIA in our cohort were more likely to develop infectious complications requiring hospitalization. We suggest to perform immunologic evaluation in all patients with MIA. Early immunodeficiency screening may help initiate appropriate intervention and improve patient outcome.
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Adrenal function assessment in children with Eosinophilic Esophagitis and prolonged treatment with swallowed topical steroids

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Objectives and Study: The purpose of this study was to measure adrenal insufficiency (AI) in children with eosinophilic esophagitis (EoE) treated with swallowed topical steroids (STS) using a standard dose (250 µg) adrenocorticotropin hormone stimulation test (SDST). Previous studies of EoE patients have reported conflicting results in relation to AI, describing prevalence between 4.7% and 65.5%.

Methods: We prospectively assessed the adrenal function in patients with EoE who were treated with STS for more than 3 months as a quality procedure in a tertiary referral centre. Children < 18 years with EoE under treatment with Oral Viscous Budesonide (OVB) or with Fluticasone Propionate (FP) for at least 3 months underwent a SDST. Normal adrenal function was stated by the Endocrinology team when peak serum cortisol was >18 µg/dL (500 nmol/L) at 60 minutes after ACTH (Synacthen®) administration or when the absolute increase from the cortisol levels at baseline was >7 µg/dL (190 nmol/L). Demographic and anthropometric data, medical and medication history, use of topical and systemic corticosteroids and endoscopic and histological findings while on STS treatment were recorded. Active EoE was defined as >15 eosinophils per high power field in oesophageal mucosa. Descriptive statistics were used for analysis and performed using SPSS version 22 (IBM Armonk, NY).

Results: We included 12 patients, 10 (83%) were male with a mean age of 10.8 years (range 6-16). All patients had a history of atopy. Two (16.7%) patients received inhaled CS for asthma treatment. None received any medications known to interfere with CYP3A metabolism. Mean treatment duration was 6.79 months (4.27-9.93). Five (41.7%) were on OVB and 7 (58.3%) on FP. OVB doses were 0.5 mg/12 hours in one (20%) child and 1 mg/12 hours in four (80%). FP doses were 250 µg/12 hours in one patient (14.3%), 400 µg/12 hours in two (28.6%) and 500 µg/12 hours in four patients (57%). Two (16.7%) had active EoE. None reported symptoms suggestive of AI and all were considered to have normal adrenal function based on the SDST results. Mean peak cortisol serum was 19.6 µg/dL (15-27.5) with a mean increase of 7.79 µg/dL (SD 3.5). Mean cortisol peak was 20.68 µg/dL (15-27) in the OVB group and 18.9 µg/dL (15-25) in the PF group.

Conclusions: This is the first study to assess adrenal function in EoE patients using the SDST (250 µg). With this method we registered normal adrenal function in all our patients after at least 3 months of STS treatment. We found no differences between FP and OVB groups. Our main limitation is the small number of subjects in the study, which prevents the extrapolation of our findings. Although the LDST is considered superior to SDST for diagnosing chronic AI, it is not available in all centers and has technical limitations. Therefore SDST could be considered as a valid test in such circumstances.
Eosinophils in the GI tract: How much is normal?

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2Centro Hospitalar São João, Porto, Portugal

Objectives and Study: The normal density of eosinophils in the digestive mucosa of children has been addressed in a small number of studies. Some of these have aimed to defining reference values. This is important to provide baseline counts as a reference for the diagnosis of eosinophilic gastrointestinal disorders (EGID). Even though histopathological criteria for EGID remains undefined, there has been a paucity in the consistency of results in different populations. We aimed to establish the eosinophil density of the normal digestive mucosa in a paediatric population submitted to endoscopic procedures that were reported as normal.

Method: Biopsies from endoscopies of 33 patients were evaluated. Quantification of eosinophils was performed manually from 4 different areas of each slide, using digital software (ImageJ) by two pathologists in a double blinded setting. Review of the pathology reports confirmed absence of abnormality in the biopsy specimens, as validated by a senior pathologist. All specimens with pathological changes (ex Inflammatory Bowel Disease) were excluded from this analysis.

Results: Oesophagus (n=33): eosinophils were uniformly absent in all biopsies. Stomach: fundus (n=14; 0.2±0.2 eos per high power field, 400x (hpf); mean±standard deviation), body (n=15; 0.1±0.1) and antrum (n=18; 0.2±0.4) revealed consistent values in the lamina propria, but no eosinophils in the surface epithelium. Small intestine: counts revealed 4.4±4.2 (maximum, 12.3), 3.6±3.0 (maximum, 10.3) and 12.6±8.6 eosinophils/hpf (maximum, 27.3) in the lamina propria of the bulb (n=13), second portion of duodenum (n=13) and ileum (n=16), respectively. Large intestine: the highest peak count was observed in the caecum (30.8; n=16) with a mean of 12.7±8.2. The eosinophil counts were lower in the ascending (n=16; 10.0±6.7), transverse (n=14; 8.4±5.4), descendent (n=15; 9.9±6.5) and sigmoid (n=17; 6.3±4.4) colon and in the rectum (n=17; 3.3±2.5). Eosinophils were regularly absent in the surface and crypt epithelium in these segments. Mean and median values were very similar in all evaluated segments.

Conclusion: These results, addressing a national population where allergy or parasitosis might differ from other countries reveal a consistent result that is comparable to previous published series, therefore adding validation of normal values. These data provide a baseline count and distribution of eosinophils in the GI tract of paediatric patients with normal histology, thus expanding the scarce published data, and provide an additional contribution to evaluate children with suspected EGID.

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Differences of microbiota in small intestine stoma effluent and colonic faeces in hospitalized paediatric patients with intestinal failure

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Objectives and Study: Several studies suggested that dysbacteriosis usually happened in patients with intestinal failure (IF). However, differences of microbiota diversity in small intestine stoma output and colonic faeces were rarely studies. Thus this study is aimed to investigate the microbiota compositions and differences of output of small intestine stoma and colon in paediatric IF patients.

Method: 24 faecal samples from 12 patients with IF were included ranging from November 2016 to November 2017. Each patient received fistula closure in our centre and faecal samples from both small intestinal stoma and colon were collected. Faecal microbial compositions were determined by high-throughput sequencing.

Results: The bacterial diversity of the small intestine stoma was significantly higher than that of colonic faeces. Stoma effluent was richer in Proteobacteria and Firmicutes and more deficient in Bacteroidetes and Actinobacteria on phylum level. Enterobacteriaceae was the most pronounced family both in stoma output and colonic faeces. Proportion of Bifidobacteriaceae was significantly higher in anus stool than that of stoma effluent. However, quantities of Comamonadaceae, Moraxellaceae and Nocardiaceae, which could be opportunistic pathogens, were larger compared with colonic faeces. In addition, higher level of Veillonellaceae was observed in stoma output and Veillonellaceae was thought to had a pro-inflammatory effect. Bacteria from Klebsiella, Lactobacillus, Veillonella, Citrobacter, Acinetobacter and Rhodococcus increased in stoma output on genus level. Function pathways of amino acid and transport and metabolism, carbohydrate transport and metabolism dominant both in microbiota of colonic faeces and stoma effluent.

Conclusion: IF patients have a marked intestinal dysbiosis characterized by Proteobacteria. Pro-inflammatory and opportunistic pathogens have a better chance to colonize if patients with IF have intestinal stoma.

![Species name](Species name)

<table>
<thead>
<tr>
<th>Species name</th>
<th>colon-Mean(%)</th>
<th>colon-Sd(%)</th>
<th>stoma-Mean(%)</th>
<th>stoma-Sd(%)</th>
<th>P value</th>
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<tr>
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</table>

[Different composition of microbiota]

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Acute gastroenteritis is a major concern for parents as a child can become critically ill and parents are unaware of alarm signs and are often unsure how to manage the symptoms. A simple key message about AGE should be transmitted widely. The rapid identification of AGE, clinical assessment with evaluation of dehydration, and rehydration with oral rehydration solutions (ORS) are the pillars of successful management. Hygiene measures are paramount to avoid contagion, however, active vaccination against Rotavirus is effective and cost-beneficial. A better understanding of the disease and its management can decrease the morbidity and mortality caused by acute gastroenteritis, and at the end, decrease relevant health care costs. A 3 minutes video was created with the aims at providing straightforward recommendations and practical tips for the management of AGE to parents.

This project created in 2016, was formed to tackle AGE in children on a global scale. One first video was produced for health professionals (“Global Burden and Management of Acute Gastroenteritis in Children: a Video for Health-Care Providers Based on International Guidelines (1)”). This video was presented at the closing ceremony of last ESPGHAN meeting and is already translated in French and Spanish. This year, the second video: “Acute Gastroenteritis in Children: a Video for Parents Based on International Guidelines” was created. The aim is to present this video to an international audience for dissemination. After that, the video will be translated into French, German, Italian, and Spanish and linked to websites of national pediatric societies and other socials networks. Both videos were produced by a group of Young ESPGHAN coming from 5 different European countries with the aid of a grant from FISPGHAN and further support from ESPGHAN and it is a spotlight to the activities of Young ESPGHAN. Cooperating working groups with the aim to represent child health on an international scale will be indispensable in the next years.

(1) https://www.youtube.com/watch?v=VBCNEATmS4w&feature=youtu.be

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**Objectives and Study:** The decreasing eradication rate of Helicobacter *pylori* is mainly because of the progressive increase of its resistance to antibiotics. Studies on antimicrobial susceptibility of *H. pylori* in children is limited. This study aimed to investigate the resistance rates and patterns of *H. pylori* strains isolated from children.

**Method:** Gastric mucosa biopsy samples obtained from children who had undergone upper gastrointestinal endoscopy were cultured for *H. pylori* and susceptibility to six antibiotics (clarithromycin, amoxicillin, gentamicin, furazolidone, metronidazole and levofloxacin) was tested from 2012 to 2014.

**Results:** A total of 545 *H. pylori* strains were isolated from 1390 children recruited. The total resistance rates of *H. pylori* to clarithromycin, metronidazole and levofloxacin were 20.6%, 68.8%, and 9.0%, respectively. No resistance to amoxicillin, gentamicin and furazolidone was detected. 56.1% strains were single resistance, 19.6% were resistant to more than one antibiotic, 16.7% for double resistance, and 2.9% for triple resistance in 413 strains against any antibiotic. And the *H. pylori* resistance rate increased significantly from 2012 to 2014. There was no significantly difference in the resistance rates to clarithromycin, metronidazole and levofloxacin between different gender, age groups, and patients with peptic ulcer diseases or non-ulcer diseases.

**Conclusion:** Antibiotic resistance was observed in *H. pylori* strains isolated from children in Hangzhou and it increased significantly during the three years. Our data strongly support current guidelines which recommend antibiotic susceptibility tests prior to eradication therapy.

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Laparoscopic assisted percutaneous endoscopic gastrostomy in children; a safe and minimally invasive procedure

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²Shaare Zedak Medical Center, Abu Dhabi, United Arab Emirates

Objectives and Study: Laparoscopic Assisted Percutaneous Endoscopic Gastrostomy (LAPEG) using a single abdominal wall port through the umbilicus is a technique that has been used for placing gastrostomies. It offers a high safety profile with the need for minimal surgical intervention. There is scarce data available in the literature on its outcome or complication rate. The outcome of such procedure will be reviewed and compared against a recently published systematic review comparing laparoscopic assisted gastrostomy (LAG) versus percutaneous endoscopic gastrostomy (PEG).

Method: This is a retrospective single centre review over a 5 year period (September 2012-2017) of all children under 16 undergone LAPEG.

Results: 54 patients were identified, 31 males. Median age at gastrostomy insertion was 1 year (range: 1 month - 14 years), with 37% of patients being less than 1 year. Median weight was 9kg (range: 2.9-29 kg) with 31% less than 7 kg. 22% of patients had previous abdominal surgery and 26% were in intensive care at the time of gastrostomy insertion. The successful completion rate was 100%. There was 0% conversion to open gastrostomy, adjacent bowel injury, intra-peritoneal leakage before the first tube change or complications that required re-intervention under general anaesthesia. Early tube dislodgement developed in 2% of patients. Median time of procedure was 35 minutes (range 9-226 minutes).

On comparison to LAG and PEG procedures using published meta-analysis data from 2017, LAPEG appears to offer less early tube dislodgement, less intraperitoneal leak before the first tube change and reduced need for re-intervention under general anaesthesia. The operating time for LAPEG is less than that reported for LAG but slightly more than that required for PEG insertion.

Conclusion: LAPEG is a safe and minimally invasive technique; it allows full and direct visualisation of the procedure throughout its entire course and hence minimal complications. It facilitates safe placement of gastrostomies in complex patients and even in low weight children and when PEG is contraindicated. One single umbilical laparoscopic port was sufficient for a successful procedure which offers a good cosmetic outcome.


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Dynamic esophageal stent OPBG: a new frontier for esophageal stenosis

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Objectives and Study: Pediatric esophageal stenoses are caused mainly by caustic ingestion and esophageal malformations. When they become refractory to dilations, esophageal stenting is considered. There are different types of stent described in literature. Custom dynamic esophageal stent OPBG was proposed as an active strategy that improves esophageal motility by leading the passage of food and liquids between the esophageal wall and the stent, inducing peristalsis and self-dilation. The new Dynamic Esophageal stent OPBG (DES) is an upgrade of custom stent. DES is an industry-built device which retains the same dynamic strategy but has a new dress: it is a polyurethane nasogastric tube with a built-in coaxial stent, flexible and atraumatic on esophageal mucosa, available in different standard sizes. The aim of the present study was to evaluate the feasibility and safety of DES for esophageal stenosis.

Method: This mono-institutional study was approved by the local Institutional Ethics Committee. Patients aged 6 months-17 years affected by scar esophageal stricture (caustic esophageal stenosis not treated or already treated with several dilations, and post-surgical stenosis treated with at least 5 dilations) were enrolled. Patients with esophageal atresia underwent angio-CT scan to rule out vascular malformations. Patients with esophageal perforations during pre-stent dilations were excluded. Stent placement and removal were performed under general anesthesia. An esophagram was performed 24h after placement to rule out leakage and to start feeding. One month after removal, another esophagram was performed to assess the length of the stenosis.

Results: The study enrolled 12 patients (6M, 6F, mean age 110.4±67.5 mos). Main etiologies were caustic injection (58%) and esophageal atresia (25%). In one case with a particularly severe stenosis, the stent was placed three times, thus 14 procedures overall were performed. One case of lusory artery was found through angio-CT and surgically treated before stenting. All the procedures were free from major complications. Two minor adverse event were registered, an esophageal leakage treated conservatively and a stent dislocation that needed repositioning. No consequences were recorded. Pre-stent length of stricture was 5.4±3.9 cm. The stent was left in place for 107 days (mean). DES determined a significant reduction in length of stricture, which was 3.0±2.3 cm post-stent (p=0.0151, paired t-test). We defined post-stent reduction of stenosis length as Δ-stenosis. A linear correlation was observed between length of stent stay and Δ-stenosis (p=0.0428, ANOVA). Stricture etiology and sex did not influence Δ-stenosis. Older age determined a nonsignificant trend to improved Δ-stenosis (p=0.059, ANOVA). As concerns stent length, stents more "tailored" to the length of stenosis outperformed those stents far longer than stricture length (p=0.0090, Mann-Whitney U test).

Conclusion: DES positioning was feasible and safe in our patients' cohort, thus meeting the primary objective of the study. Moreover, DES was effective in reducing the length of esophageal stenosis. Therefore, this new device deserves validation in a multicenter effort involving tertiary-level institutions to further assess its role in the treatment of esophageal stenosis.

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Endoscopic sphincterotomy in acute recurrent and chronic pancreatitis in children

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Objectives and Study: Acute recurrent and chronic pancreatitis in children are associated to genetic mutations, such as cationic trypsinogen protease serine 1 (PRSS1), serine protease inhibitor, Kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator gene (CFTR), and chymotrypsin G (CTRG) mutations. International literature still debates regarding the endoscopic sphincterotomy that usually is indicated in patients with higher burden of attacks. In our series, we evaluate how ERCP with pancreatic sphincterotomy and stent placement can improve symptoms and reduce episodes of pancreatitis in genetic pancreatitis in children.

Method: From 2012 to 2017, a total of 42 patients with acute recurrent and chronic pancreatitis with genetic mutations were identified and stratified in our centre. Sex, age, genetic mutation type, radiological investigations, endoscopic retrograde cholangiopancreatography (ERCP), pancreatic sphincterotomy, pancreatic stent placement, clinical outcome post-endoscopic sphincterotomy (no/pancreatitis with hospitalization) were evaluated.

Results: We enrolled 42 patients (F/M: 21/21; mean age 17 years). All patients presented genetic mutations: 35 CFTR-related, 5 PRSS1, and 2 SPINK1. All patients had Ultrasound and Secretin Magnetic Resonance Cholangio-Pancreatography (MRCP), which documented Wirsung dilatation and dis-homogeneous pancreatic parenchyma. 24 patients (57%; F/M 10/14 mean age 17 years) underwent endoscopic pancreatic sphincterotomy because severe disease course; a pancreatic stent was placed in 15 (63%) out of 24 patients, instead 9 (37%) patients had only pancreatic sphincterotomy. 4 patients (4/24-16%) had more than one sphincterotomy. It has been reported significant abdominal pain in 2 patients, iatrogenic pancreatitis in 4 patients, 1 patient abdominal spill in 1 patient, bleeding in 1 patient, in the 24 hours after sphincterotomy. The remaining 18 patients (43%; F/M 11/7; mean age 13 ys) never had ERCP because a good disease course. We observed a reduction in the number of attacks and hospitalization in in 19 patients (19/24 - 79%).

Conclusion: Endoscopic sphincterotomy is a valid treatment strategy to improve clinical symptoms and reducing attacks and hospitalizations.

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A paediatric tertiary multicenter cohort comparison of elective gastrostomy outcomes in children

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Objectives and Study: There is significant evidence in adult patients comparing outcomes from percutaneous endoscopically placed gastrostomies (PEG) favorably with laparoscopic and open gastrostomy techniques. The literature in children has been dominated by single center studies and to date there has not been a cost analysis differentiating the several techniques. This study aimed to retrospectively analyze and compare the outcomes defined by complications, mortality, and cost between PEG and non-PEG gastrostomies performed in the paediatric population served by a large collaborating group of tertiary paediatric centers in the United States.

Method: All PEG (ICD-9-PCS 43.11) and non-PEG (ICD-9-PCS 43.0 & 43.19) gastrostomies in children on their first or second day of admission and during 2010-2015 were abstracted from the Pediatric Health Information System (PHIS) database, a comparative database with clinical and resource utilization data from >45 children’s hospitals in the United States. Data abstracted from each encounter included demographic, insurance group, and medical comorbidities, as well as procedure type, hospital, procedure year, 30 day readmission, as well as presence of second procedure (defined as another gastrointestinal procedure performed during the same admission, but not the same day, as the gastrostomy). The effects of gastrostomy type on mortality and 30-day readmission, adjusting for patient demographics and healthcare setting, were determined using a forward, stepwise binary logistic regression model, with variables having p< 0.05 remaining in the model. Generalized linear models were used to determine the effect of gastrostomy type on length of stay and total cost.

Results: Out of 11,712 gastrostomy cases, 3,160 cases (27%) were PEG. Among all cases, the incidence of mortality was 100 cases (0.85%). Gastrostomy choice was not a significant factor associated with mortality (p = 0.153), although neonatal (p = < 0.001; OR = 3.72 (2.28 - 6.05)), cardiovascular (p < 0.001; OR = 2.49 (1.57-3.94)), and genetic (p < 0.001; OR = 1.96 (1.24-3.10)) comorbidities were significant. Among all gastrostomies, 3,460 cases (31.2%) were readmitted within 30 days, with lower risk of readmission associated with PEG gastrostomy (p< 0.001; OR 0.74 (0.67-0.82)). Additional factors increasing risk of readmission include malignancy (p< 0.001; OR 5.05 (4.12-6.09)), and performing second GI procedure on admission (p = 0.007; OR 1.33 (1.08 - 1.64)). Median length of stay was 3 days (IQR 2- 5 days). Median cost of visit was $30,283 (IQR $19,435 - $55,335). Choice of gastrostomy was not a significant factor in the variation in length of stay (p = 0.992) nor the total cost of admission (p = 0.996).

Conclusion: Gastrostomy placement techniques in children are generally safe. A limiting factor in this analysis was the significant confounding effect of simultaneous but unrelated procedures. The differences in clinical outcome and cost between PEG and non-PEG gastrostomy is marginal, favoring PEG, with no significant effects found on mortality, length of stay, and total cost, and a slightly lower risk of readmission with PEG.
<table>
<thead>
<tr>
<th>ICD-9-PCS</th>
<th># of Procedures Performed</th>
<th>Procedure Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4292</td>
<td>125</td>
<td>Dilation of esophagus</td>
</tr>
<tr>
<td>4514</td>
<td>73</td>
<td>Closed [endoscopic] biopsy of small intestine</td>
</tr>
<tr>
<td>4513</td>
<td>60</td>
<td>Other endoscopy of small intestine</td>
</tr>
<tr>
<td>5498</td>
<td>59</td>
<td>Peritoneal dialysis</td>
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<tr>
<td>5459</td>
<td>56</td>
<td>Other lysis of peritoneal adhesions</td>
</tr>
<tr>
<td>4632</td>
<td>35</td>
<td>Percutaneous (endoscopic) jejunostomy (PEJ)</td>
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<tr>
<td>4562</td>
<td>35</td>
<td>Other partial resection of small intestine</td>
</tr>
<tr>
<td>4516</td>
<td>29</td>
<td>Esophagogastrroduodenoscopy (EGD) with closed biopsy</td>
</tr>
<tr>
<td>4251</td>
<td>23</td>
<td>Intrathoracic esophagoesophagostomy</td>
</tr>
</tbody>
</table>

[Most Common Second Procedures with Gastrostomy]

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Validation of Direct Observation of Procedural Skills (DOPS) for paediatric gastroscopy

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Objectives and Study: Direct observation of procedural skills (DOPS) are tools designed by the Joint Advisory Group (JAG) to assess competence in endoscopy. These were expanded in July 2016 (new DOPS) to include those specific to paediatric gastroscopy (OGD). However, paediatric OGDDOPS assessments have not been validated. Aim of study - To correlate overall trainee competence with components of the paediatric OGD DOPS.

Method: We performed a prospective UK-wide analysis of formative paediatric OGDDOPS submitted to the JETS e-Portfolio over one-year (August 2016-2017). Scores were averaged across procedural domains (pre-procedural, procedural, post-procedural and endoscopic non-technical skills - ENTS). Each DOPS item, except for ENTS, were grouped into cognitive and technical skillsets by two independent investigators, and correlated with the overall performance score. Correlation analyses were performed using Spearman's test (rho >0.70 indicating high positive correlation).

Results: 157 DOPS assessments were completed by 20 unique trainers for 17 trainees. Overall performance score comprised: 1: Maximal supervision (4.5%), 2: Significant supervision (14.0%), 3: Minimal supervision (24.8%) and 4: Competent (56.7%). By domain, overall competence correlated most with mean scores for the 'Insertion and Withdrawal' domain (rho: 0.884, p&LT; 0.001), followed by 'Management' (rho 0.834, p&LT; 0.001), 'Visualisation' (rho 0.819, p&LT; 0.001), ENTS (0.773, p&LT; 0.001), 'Post-procedural' (rho 0.611, p&LT; 0.001) and 'Pre-procedural' (rho 0.575, p&LT; 0.001) domains. By skillset, overall score correlated most with performance in 'Technical' (rho 0.860, p&LT; 0.001), followed by ENTS and 'Cognitive' domains (rho 0.788, p&LT; 0.001) domains. There was strong correlation between cognitive and ENTS skillsets (rho 0.852, p&LT; 0.001). In terms of DOPS items, overall competence score correlated most with 'Management of Complications' (rho 0.852, p&LT; 0.001) and 'Angulation and Tip Control' (rho 0.834, p&LT; 0.001), and least with 'Confirms Consent' (rho 0.396, p&LT; 0.001) and 'Equipment Check' (rho 0.528, p&LT; 0.001).

Conclusion: Our data identify the aspects of OGD which assessors relate most closely with overall competence. In OGD, performance in the 'Insertion and Withdrawal' domain, 'Management of Complications' items, and 'Technical' skill sets had greatest correlation with overall procedural competence. Competencies in paediatric OGD, as assessed within DOPS, vary in their correlation with overall competence. As assessors are completing the new DOPS in a consistent manner, this provides novel validity evidence for the new paediatric OGD DOPS.

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GASTROENTEROLOGY - Endoscopy

G-eP-036

Is there any place for the use of narrow band imaging (NBI) in routine gastrointestinal paediatric endoscopy?

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Background: Imaging systems such as NBI can be used in endoscopy and may affect its effectiveness. However, it's crucial to take time to become acquainted with this new imaging system.

Objective: To evaluate the use and utility of NBI in routine paediatric endoscopy.

Design: Retrospective study.

Setting: Tertiary care centre. The endoscopic examinations using an “Olympus Evis Exera III” video imaging system and 190 series scopes were reviewed. All examinations were performed by the authors. The patients and images that were evaluated with both NBI and white light imaging (WLI) were selected. Indication for endoscopy, endoscopic diagnosis, differences in mucosal morphology and vascularity between conventional endoscopy and NBI were evaluated. Histological findings were reviewed.

Results: During a 2-year period, 409 patients were submitted to 536 upper endoscopies. Both NBI and WLI were used and compared in 316 upper endoscopies (59%). In the same period, 98 patients were submitted to 110 colonoscopies. In 21 (19%) both NBI and WLI were used and compared. Male/Female ratio was 1.19:1.0 and 1.58:1.0, and the mean age ± standard deviation (SD) was 9.8 ± 5.6 and 11.4 ± 5.6 years for upper endoscopy and colonoscopy, respectively. Oesophagus mucosa was evaluated with NBI in 299 examinations, being the most evaluated mucosa by this technique (95%). It was normal in 135 and had lesions in 164 (erosive reflux disease (ERD), 54; eosinophilic oesophagitis (EoE), 48; Barrett's oesophagus, 21; ectopic gastric mucosa, 12; others, 29). Gastric mucosa was only evaluated with NBI in 15 examinations, being normal in 4 and with lesions in 11 ("gastritis", 8; polyps, 3). Of the 34 duodenal examinations with NBI, 22 had normal mucosa and 12 had lesions (erosion and ulcer, 8; coeliac disease, 2; ectopic gastric mucosa, 1; polyps, 1). Of the 21 colonoscopies in which NBI was used, 13 had IBD with superficial erosions and the remaining had normal mucosa. Small mucosa breaks as well as oesophageal micro-erosions were more readily discerned with NBI, improving the endoscopic diagnosis of ERD and of EoE. Squamocolumnar junction and the presence of abnormal mucosal islands, Barrett's oesophagus and ectopic gastric mucosa were visualized more precisely with NBI. The gastric and duodenum images obtained with NBI were of little practical use. NBI was useful for the diagnosis of IBD with normal mucosa seen with WLI, but with superficial erosions seen with NBI.

Conclusion: NBI improves the accuracy of endoscopic diagnosis and may be of interest in the diagnostic accuracy of oesophageal and colic disease in paediatric age, and probably will soon become an essential tool of endoscopic examination. Then, a standard education programme of NBI in paediatric endoscopy will be needed.

Key words: endoscopy, narrow band imaging (NBI), white light imaging (WLI).

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Monitoring the quality of life in dyspeptic patients with KINDL scale

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Objectives and Study: Children with dyspepsia has lower quality of life compared to heathy children. However scarce data is available about the change in quality of life in these children after treatment. In this study, monitoring the quality of life in patients who have been followed up for functional and organic dyspepsia by age appropriate KINDL scale and evaluating the difference in quality of life during follow-up between these two groups were aimed.

Method: Patients between 4-17 years of age, who admitted to the Pediatric Gastroenterology outpatient clinic with dyspepsia were enrolled. Abdominal pain, heartburn, nausea, vomiting, abdominal distension, regurgitation, chestburn, flatulence were accepted as dyspeptic complaints. Patients who did not come to the follow up visits regularly and with chronic diseases which may affect the quality of life were excluded from the study. The discrimination of organic and functional dyspepsia was done according to the existence of alarm symptoms and the result of upper gastrointestinal endoscopy, if it was applied. At the first visit and at controls of 1st and 3rd months, KINDL was applied. Demographic data, symptoms and quality of life scores were compared between functional and organic dyspepsia groups. Change in quality of life scores within the groups were also evaluated.

Results: A total of 136 patients (71 functional dyspepsia, 65 organic dyspepsia) were included in the study. Mean age of patients was higher in organic dyspepsia group. There was no difference in localization of abdominal pain, mean duration of complaints, symptom rate and frequency between organic and functional dyspepsia groups. There was no difference in terms of school absenteeism between these groups either. Mean scores in physical wellness and school subgroups were higher among functional dyspepsia group than organic dyspepsia group. There was no difference in terms of emotional wellness, self-esteem, family and friends subgroups. Total score of patients in functional dyspepsia group were higher. There was no relation between gender, number of symptoms, maternal education level and paternal education level with KINDL scores. At the first month follow up visit, total scores and mean scores of self-esteem, family, school and friends subgroups were higher in functional dyspepsia group. In the third-month follow-up visit, mean score of self-esteem was higher for the patients with functional dyspepsia. Total scores increased significantly during follow up in both organic and functional dyspepsia groups. The increase among the patients in organic dyspepsia group was higher than functional dyspepsia group.

Conclusion: The quality of life for both functional and organic dyspepsia groups are affected. Functional gastrointestinal diseases, which are not considered important as there is no underlying organic diseases, were also found to be affecting the quality of life. Thus, we suggest to give the necessary instructions and treatment. Instructions and treatments increase the quality of life of these patients. Positive results may be obtained when treatment for the underlying disease was given to the patients with organic dyspepsia. Treatment is essential for both groups and quality of life scales may be used to follow the response to treatment.

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Predictive and associated factors for early antireflux surgery in oesophageal atresia excluding long gap

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Objectives and Study: Oesophageal Atresia (OA) is a rare congenital malformation. Gastroesophageal reflux disease (GORD) is the most frequent complication and occurs in 25 to 63% after repair of OA and can lead to severe complications. The aim of this study was to identify predictive and associated factors for antireflux surgery in the first year in patients included in the French register of OA excluding long gap.

Method: All 38 multidisciplinary French centers that care for patients with OA returned a specific questionnaire about the 1-year outcome for each patient. The register was approved by the National Informatics and Privacy Committee (CNIL), and was qualified by the National Committee of Register (InVs, CNR) according to international ethical standards. Data collected included neonatal characteristics of the patient and information about OA surgery. Outcome up to 1 year of age was assessed including treatment, complications and nutritional status. We identified predictive factors, defined as factors existing since birth and characteristics of oesophageal atresia surgery. Associated factors were defined as other factors/complication appearing after OA surgery in the first year of life.

Results: From the total population of 835 OA born between 2010 to 2014 in France, 682 patients had OA excluding long gap (sex ratio M/F: 1.49). Three patients had type I EA, 669 patients had type III EA and 10 patients had type IV EA. 36% of cases were born at gestational age< 37 weeks, with a mean birthweight z-score of -1.70 ± 1.52 (median, 1.6; range, -5.9 to 2.0). The median age of end to end esophageal anastomosis was 1.1 day (range: 0 to 15). During the first year of life, antireflux surgery was performed in 53 infants, (one-year rate, 7.8%, 95%CI, 5.9 to 10.0%), at a median age of 135 days (range: 22 - 357). We identified in multivariate analysis, three predictive factors of early antireflux surgery: anastomotic tension (p = 0.004), associated malformations (p = 0.019) and low birth weight (p = 0.018) and six associated factors with antireflux surgery: anastomotic stenosis (p &LT; 0.001), gastrostomy (p &LT; 0.001), acute life-threatening event (p = 0.002), respiratory complication (p &LT; 0.001), GORD (p &LT; 0.001) and poor nutritional status (p &LT; 0.001).

Conclusion: Early antireflux surgery is frequent in OA population. Identifying predictive and associated factors for antireflux surgery helps in the care of this fragile population.

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Anastomotic strictures in patients with oesophageal atresia systematically treated with PPI: prospective cohort study over 10 years

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Objectives and Study: Clinical course in oesophageal atresia (OA) patients with or without tracheo-oesophageal fistula (TOF) is frequently complicated by gastroesophageal reflux disease (GORD), which is classically thought to be a risk factor for formation of anastomotic strictures. It is therefore currently recommended that OA patients be treated systematically with proton pump inhibitors (PPI) after surgical oesophageal repair. However, it is not clear, if PPI treatment does really prevent the formation of anastomotic strictures. We aimed to describe the outcomes of a cohort of OA-TOF patients systematically treated with PPI since the neonatal period. We hypothesize that systematic PPI treatment prevents anastomotic stricture occurrence.

Method: Prospective longitudinal cohort study of 73 children with OA-TOF, born between September 2005 and December 2014 and systematically treated with PPI. Outcome was evaluated at study end in February 2017. The incidence of anastomotic strictures was compared to a historical cohort of 134 OA patients followed in the same institution between 1990 and 2005 before the era of systematic PPI treatment.

Descriptive data are presented as median [interquartiles] for continuous variables and as frequency (%) for categorical variables. To compare groups, Pearson's χ² test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were used. All analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC); P values < 0.05 were considered statistically significant for all analyses.

Results: 73 patients (41 males) were included in the final analysis. Median age at study completion was 4.67 years [3.64, 7.97; range 1-11.4]. According to Gross classification, 64 patients (88%) had OA type C, 8 (11%) had type A, and 1 (1%) had type D; long gap OA was present in 16 patients (22%). Thoracotomy was performed in 56 patients and thoracoscopy in 17. Anastomotic strictures and recurrent strictures were diagnosed in 32 (44%) and 17 patients (23%), respectively. In all but one cases, strictures occurred when the child was on PPI. Characteristics and outcomes of OA patients with anastomotic strictures are compared with patients without strictures. Anastomotic strictures occurred significantly more frequent in long gap OA, in patients with anastomotic leak after surgical repair and longer hospital stay (p=0.02, 0.002 and 0.02 respectively). Histological complications, especially gastric metaplasia, appeared more frequently in OA patients with anastomotic strictures (p=0.01).

The incidence of anastomotic strictures was comparable to a previously published study of 134 OA-TOF patients not systematically treated with PPI (32 (44%) vs 52 (39%); p>0.05), conducted in our institution between 1990 and 2005.

Conclusion: Long gap OA and presence of anastomotic leak after surgery are associated with the occurrence of anastomotic strictures. PPI treatment does not prevent the formation of anastomotic strictures and histological complications appeared more frequently in patients with strictures, despite PPI treatment. A more selective prescription of PPI is proposed.

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Eosinophilic esophagitis in esophageal atresia: a retrospective chart review of a tertiary care referred children

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Objectives and Study: Although survival rate dramatically improved over the last decades, digestive and respiratory comorbidity negatively affects quality of life of patients underwent repair of esophageal atresia (EA). Anastomotic stricture and esophageal dysmotility-related conditions, such as gastroesophageal reflux disease (GERD) and dysphagia, are the most frequent GI complications, but emerging data are also reporting a higher prevalence of eosinophilic esophagitis (EoE) in EA patients than general population. Aim of the study was to describe and analyze disease characteristics of EA children with EoE.

Method: A retrospective chart review from January 2005 of both children with EA and EoE in follow-up at Bambino Gesù Children's Hospital in Rome has been performed. EoE was defined as esophageal eosinophilic inflammation with ≥15 eosinophils per high-power field [EOS/HPF]. In EA patients (born since 1995), as per hospital protocol, esophageal biopsy specimens were collected only in case of esophageal symptoms recurrence not attributable to other cause (e.g. anastomotic stricture) or in the presence of endoscopic features suggestive of EoE. Patients showing eosinophilic inflammation received treatment with proton-pump inhibitors (PPIs) and those achieving clinical, endoscopic, and histologic response to were defined as PPI-responders. Those non-responders to PPIs underwent to dietary and/or topical steroid treatment. Demographics and disease characteristics of EA patients with EoE (Group EA-EoE) were analyzed and compared with those with EoE from general population (Group EoE).

Results: Overall, 370 EA and 118 EoE patients were analyzed. Of them 15 EA-EoE patients were detected (4 long gap EA). Consequently, in our cohorts, 4.0% of EA patients have developed EoE and 12.7% of EoE children had a previous history of EA repair. Among EoE, male-to-female prevalence ratio was of 2.55 (p<0.0001) with no difference in gender prevalence between groups. At diagnosis EoE-EA children were significantly younger compared to EoE group (mean: 5.1 vs 10.8 years; p=0.0001). Peak EOS/HPF at diagnosis did not differ between groups (50.1±26 vs 59.8±29 EOS/HPF). Overall, 65.8% of children reported allergies (both ood and aero allergy) with no difference between groups (53.8 vs 68.0%). Patients PPI-responder were significantly more prevalent in EA-EoE group that in EoE group (66.6% vs 19.4%; p=0.0004). Among non-PPI-responders, all but one EA-EoE patient (long gap EA) are on disease remission.

Conclusion: Although to a lesser extent than previous reports (~17%), our data confirm that EA patients are more prone to develop EoE than general population (~0.05%). Patients with EA received EoE diagnosis at younger age than general population. Moreover, EA patients were more likely to reach complete disease resolution after PPI trial. Similar gender distribution and high prevalence of allergy suggest that common genetic susceptibility factors for EoE exist. However, high incidence and early onset of EoE coupled with high prevalence of PPI-responders, seen in EA children, might also suggest that esophageal motility disorders might interact to increase propensity to EoE in EA patients. In EA, GERD and impaired esophageal clearance are more likely to play a pivotal role in EoE pathogenesis than general population.

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Trends in incidence of celiac disease autoimmunity in a large health maintenance organization

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Objectives and Study: Incidence and prevalence rates of Celiac disease (CD) are increasing worldwide in the last decades, with estimated prevalence of 0.3%-3%. In Israel, the prevalence of CD was recently estimated at 1.1%. Our aim was to explore large-scale data regarding trends in incidence of CD autoimmunity in Israel in the last decade.

Methods: Maccabi Healthcare Services (MHS) is a 2-million-member health maintenance organization in Israel which are representative of the Israeli society in terms of age, sex and socio-economic status. We retrospectively retrieved all CD serology tests includes: tissue transglutaminase (tTGA-IgA), anti endomysial and deamidated gliadin peptides antibodies, that were performed between 2005-2015 from MHS central databases. We specifically examined first time seropositive results and excluded those who had positive results before this time period.

Results: Incidence of CD autoimmunity, defined as first seropositive result per individual, increased from 17.7 per 100,000 population to 51.8 per 100,000 population during the years 2005-2015 (p < 0.0001, R²=0.9, Figure 1). A sub analysis of tTGA positive levels during 2012-2015 revealed that 47% were greater than 10 times the normal range, 12% were 5-10 times normal range, 10% were 3-5 times normal range and 31% were lower than 3 times the normal range. These proportions have not changed over time.

Conclusion: Incidence of CD autoimmunity increased significantly during the last decade with no change in the pattern of high positive serology levels.

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Objectives and Study: Coeliac disease (CD) is associated with HLA-DQ2 and DQ8 found in more than 95% of European patients. Few genetic studies performed in different Russian regions and former Soviet republics demonstrated the prevalence of DQ2/DQ8 alleles in children with CD as 60-80% with speculations that coeliac genotype might have regional differences and a certain part of Russian patients can develop the disease without DQ2/DQ8. The aim of our study was to determine the distribution of HLA-DR-DQ genotypes in coeliac children diagnosed in Moscow clinics.

Method: We performed genetic typing in 70 children with CD and divided patients into genetic risk groups as suggested in former European studies (high - DR3-DQ2/DR3-DQ2, DR7-DQ2/DR7-DQ2, DR3-DQ2/DR7-DQ2; substantial - DR3-DQ2/DR5-DQ7, DR7-DQ2/DR5-DQ7; moderate - DR3-DQ2/DRx-DQx, DR3-DQ2/DR4-DQ8; low - DR7-DQ2/DRx-DQx, DR7-DQ2/DR4-DQ8, DR4-DQ8/DRx-DQx, DRx-DQx/DRx-DQx).

Results: Sixty eight children (97.2%) were HLA-DQ2/DQ8 positive. Among them 85.3% were DQ2 positive, 8.8% - DQ8 positive, 5.9% patients carried both DQ2/DQ8 molecules. Among 58 DQ2 positive patients 25.7% were DQ2 homozygous (DR3-DQ2/DR3-DQ2 - 3.4%, DR7-DQ2/DR7-DQ2 - 1.7%, DR3-DQ2/DR7-DQ2 - 20.6%). Other DQ2 positive patients presented with following distribution of HLA-DR-DQ alleles: DR3-DQ2/DR5-DQ7 - 15.5%, DR7-DQ2/DR5-DQ7 - 17.2%, DR3-DQ2/DRx-DQx - 17.2%, DR7-DQ2/DRx-DQx - 6.9%. Ten patients had incomplete DQ2 molecule presented with DQA1*0501 allele, though nine of these patients had DQA1*0501 linked with DQB1*0301 encoded DR5-DQ7 molecule. We found high and substantial risk alleles in 21.4% and 27.1%, and moderate and low risk alleles in 17.1% and 34.4% respectively.

Conclusion: We found the same as European prevalence of DQ2/DQ8 in Russian children with CD with almost equal number of patients carrying high-substantial or moderate-low risk alleles.

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Longitudinal analysis of intestinal biopsies from children with potential coeliac disease: immunohistochemical markers predicting evolution to villous atrophy

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**Objectives and Study:** The term potential coeliac disease (PCD) describes subjects with a normal small intestinal mucosa architecture and positive CD serology. Some have a completely normal mucosae (Marsh 0), others have an infiltrative lesion (Marsh1). The natural history of this condition is still unclear; however, previous observations showed that at 9 years of follow-up 67% of them still have normal duodenal architecture. Aims of this study were first to compare immunohistochemical features of Marsh 0 vs Marsh 1 PCD, second to identify immunohistochemical markers predicting evolution to villous atrophy.

**Method:** 96 sequential biopsies were obtained from 32 PCD patients: 32 and 52 duodenal biopsies showed Marsh 0 and Marsh 1 (IELs > 34 cell/mm of epithelium) respectively. At least three biopsies were taken from each patient during the follow-up (median follow-up: 5 years and 10 months); 12 patients eventually developed villous atrophy. Number of CD3+, TCR-γδ+ and cytotoxic lymphocytes (perforin+ cells) in the epithelial compartment, and density of CD25+ cells in the lamina propria were evaluated by immunohistochemistry. Furthermore, the expression of pro-inflammatory cytokines such as IL-15 and IL-21 was also investigated.

**Results:** In the epithelium compartment of Marsh 1 PCD not only CD3+ IELs, but also TCR-γδ+ were significantly increased in comparison with PCD Marsh 0 patients (p<0.0001), the TCR-γδ+/CD3+ ratio being not different. Interestingly, the density of perforin+ cytotoxic cells was significantly increased in PCD Marsh 1 mucosae if compared with PCD Marsh 0 (p<0.0001), although lower than in patients with active CD (p<0.0001). In the lamina propria the number of mononuclear CD25+ cells was comparable in Marsh 0 and Marsh 1 PCD. Furthermore also IL15 and IL21 expression did not show differences both in the surface epithelium and in the lamina propria. When analyzing the biopsies prospectively, those who developed villous atrophy had an increased CD3+ IEL density and TCR-γδ+/CD3+ ratio in the biopsies taken at enrollment. Stepwise canonical discriminant analysis indicated TCR-γδ+ IEL density as the best predictor of development of villous atrophy followed by villous/crypt ratio, epithelial expression of IL-15 and lamina propria expression of IL-21.

**Conclusion:** PCD patients with Marsh 1 mucosae show higher density of TCR-γδ+ and perforin+ cells, but no more inflammation in lamina propria when compared to Marsh 0 mucosae. TCR-γδ+ infiltration seems to be the best marker predicting evolution to villous atrophy.
Objectives and Study: Because of their increased risk for coeliac disease (CD), ESPGHAN and other guidelines advise to screen children with affected first-degree relatives. However, in the literature there is little information about the benefit of early diagnosis and treatment in these children. Our aim was to prospectively assess whether children from coeliac families benefit from screening, early diagnosis and treatment.

Methods: We analyzed the data from the European, multicentre PreventCD cohort involving 944 newborns recruited from 2007-2010, who are being prospectively assessed for CD development. All the children are positive for HLA-DQ2 and/or HLA-DQ8 and have at least one first-degree relative with CD. Health status using (parental) questionnaires on CD-related symptoms and CD antibodies (IgA against transglutaminase 2 (TGA)) were assessed at the age of 4, 6, 9, 12, 18, 24 and 36 months, and thereafter at least every two years (www.preventcd.com). TGA was centrally measured using from 2007-2014 the Celikey Varelisa test and from 2015, the Celikey ELIA method, with cut-off values of 5 U/ml and 7 U/ml respectively. If the children presented symptoms and/or increased TGA level indicating CD, diagnostic small bowel biopsies were offered. The biopsies were assessed centrally by an independent pathologist blinded to the clinical and antibody results. All CD diagnoses were discussed and agreed upon by the diagnostic committee of PreventCD. Measured outcomes were improvement of the reported symptoms and of TGA level on a gluten-free diet (GFD) at follow up 1 and 2 years after diagnosis.

Results: As on 01 December 2017, 130 children (mean age: 9.1 years; range: 7.3-10.9; 59.8% female) had been diagnosed with CD at a mean age of 3.8 years (range: 1.1- 9.2). Since 4 asymptomatic CD children did not follow a GFD, 126 CD children were included in this analysis. Seventy-one children (56.3%) were symptomatic at diagnosis and reported one or more symptoms, as shown in the table. In total 80.0% and 87.8% of the symptomatic children at diagnosis were symptom-free after one and two year on a GFD, respectively. All symptoms at diagnosis, except constipation and vomiting, significantly improved after treatment. The mean TGA level in symptomatic children decreased from 81.2 U/mL to 4.0 U/mL and 2.2 U/mL after one and two year of treatment, respectively.
<table>
<thead>
<tr>
<th>Symptoms in 126 included children*</th>
<th>At diagnosis - no. (%) N=71</th>
<th>After one year (mean 11.3 months) no. (%) N=12**</th>
<th>After two years (mean 30.0 months) no. (%) N=10***#</th>
<th>p-value (diagnosis-two years after GFD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>29 (40.8)</td>
<td>4 (6.7)</td>
<td>1 (1.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (36.6)</td>
<td>5 (8.3)</td>
<td>4 (7.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Failure to thrive§</td>
<td>23 (32.4)</td>
<td>2 (3.3)</td>
<td>2 (3.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>21 (29.6)</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (18.3)</td>
<td>2 (3.3)</td>
<td>1 (1.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other¥</td>
<td>11 (15.5)</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (14.1)</td>
<td>1 (1.7)</td>
<td>3 (5.3)</td>
<td>0.159</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (5.6)</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td>0.321</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

*One or more symptoms;**12/60 children had symptoms after one year on a GFD;*** 10/57 children had symptoms after two years on a GFD;#3 children with less than 2 years GFD after the diagnosis;§FTT= reduction of 0.5 SD weight/length per six months and/or length < -2SD);¥Other = extra-intestinal symptoms e.g. irritability, fatigue

**Conclusion:** Our prospective data show that most children from CD families develop the disease very early in life and about half of them have CD-related symptoms that improve significantly after treatment with a GFD. These results support early screening, diagnosis and treatment in children from CD families.

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Gluten intake in early childhood and risk of coeliac disease: A nationwide cohort study

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²University of Colorado School of Medicine, Aurora, United States
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Objectives and Study: Coeliac disease may occur in genetically predisposed individuals exposed to gluten. Few studies have examined if the amount of dietary gluten influences the risk of coeliac disease. Whether age at gluten introduction is associated with the risk of disease is unclear from observational studies, and not found to be a predictor in randomized trials. In this first nationwide cohort, we studied whether the amount of gluten predicts coeliac disease, and whether age at gluten introduction modifies the potential association.

Methods: The nationwide Norwegian Mother and Child Cohort Study collected prospective data on gluten intake at age 18 months using a parental questionnaire, in children born during 2000-2009. We identified clinically diagnosed coeliac disease from the Norwegian Patient Register, in addition to parental questionnaires at child age 7 and 8 years. Of 67,631 children, 761 were identified with coeliac disease by December 31ˢᵗ, 2016 (mean follow-up 11.5 years; range 7.5-15.5). We used binary regression to estimate relative risks, and adjusted for age at gluten introduction, duration of breastfeeding, parental coeliac disease, child's sex and age at end of study.

Results: The mean daily gluten intake at 18 months was 8.8 g (SD 3.6). The adjusted relative risk (aRR) of coeliac disease increased by 1.11 (95% CI 1.04-1.18) per standard deviation increase in daily gluten amount at age 18 months (Figure). Children in the upper compared to the lower quartile of gluten intake had an increased risk of coeliac disease in adjusted models (aRR 1.32, 95% CI 1.08-1.61). There was no difference in risk between children in the first and second quartile of gluten intake, suggesting a possible threshold effect of gluten intake above the median intake level. Introduction of gluten ≥6 months compared to 4-6 months was an independent risk factor (aRR 1.39, 95%CI 1.14-1.69), with no significant interaction with the amount of gluten. In exploratory analyses, children above median gluten intake at 18 months and with introduction starting ≥6 months age had an adjusted RR of 1.8 (95% CI 1.4-2.4) for coeliac disease compared to children below median intake and with introduction from 4-6 months. We were able to adjust for HLA- and non-HLA genetic risk in a nested case-control sample from the cohort (n=268 cases, n=430 controls), and adjustment for genotype did not change the main associations.

Conclusion: In our large nationwide cohort, children with gluten intake above the median at 18 months of age had an increased risk of coeliac disease, and late introduction of gluten was an independent risk factor.
Did not develop CD  n = 66,879 (%)  Developed CD  n = 761 (%)  aRR (95% CI)  RR (95% CI)

<table>
<thead>
<tr>
<th>Quartile of gluten intake g/d</th>
<th>Did not develop CD</th>
<th>Developed CD</th>
<th>aRR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (&lt;6.22)</td>
<td>16,673 (25)</td>
<td>166 (22)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>2nd (6.22-8.16)</td>
<td>16,740 (25)</td>
<td>163 (21)</td>
<td>0.99 (0.80, 1.22)</td>
<td>0.98 (0.79, 1.21)</td>
</tr>
<tr>
<td>3rd (8.15-10.68)</td>
<td>16,724 (25)</td>
<td>204 (27)</td>
<td>1.23 (1.00, 1.50)</td>
<td>1.22 (1.00, 1.50)</td>
</tr>
<tr>
<td>4th (10.68-12.22)</td>
<td>16,727 (25)</td>
<td>228 (30)</td>
<td>1.32 (1.08, 1.51)</td>
<td>1.36 (1.12, 1.60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at gluten introduction</th>
<th>Did not develop CD</th>
<th>Developed CD</th>
<th>aRR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 months</td>
<td>440 (0.7)</td>
<td>5 (0.7)</td>
<td>1.43 (0.58, 3.52)</td>
<td>1.39 (0.57, 3.38)</td>
</tr>
<tr>
<td>4-6 months</td>
<td>15,073 (23)</td>
<td>125 (16)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>51,357 (77)</td>
<td>633 (83)</td>
<td>1.39 (1.14, 1.69)</td>
<td>1.60 (1.24, 1.82)</td>
</tr>
</tbody>
</table>

[Figure: Risk of coeliac disease by daily gluten intake at age 18 mo and age for gluten introduction]

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Intracellular pathways of gliadin and microbial transglutaminase differ in duodenal epithelium after simultaneous incubation of these antigens

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Objectives and Study: Cross presentation (XPT) of antigens to T cells could play a role in pathogenesis of coeliac disease (CD). As a prerequisite for XPT, exogenous antigens like gliadin or microbial transglutaminase (mTG) have to be transported to the endoplasmic reticulum (ER), where they are loaded on MHC class I molecules. Recently, the food technological additive mTG has come to the fore, since it is able to de- and transamidate gliadin peptides like human tissue transglutaminase (TG2), the central autoantigen in CD. This study aimed to investigate differences in the intracellular pathways of mTG or gliadin using single and simultaneous incubation of these proteins within intestinal biopsies.

Method: Apical incubation of duodenal biopsies from CD and non-CD (NCD) patients was performed using mm-diameter circular aperture sliders. The mucosa was incubated either with mTG or a pepsin/trypsin digest of gliadin (Frazer’s Fraction, FF) or a mixture of both. Colocalization was done using the ER marker protein disulfide isomerase (PDI). Evaluation of the intracellular distribution of both protein fractions in normal enterocytes (NE) as well as in so-called RACE cells (rapid uptake of antigen into the cytosol of enterocytes) was carried out on an electron microscopical level using immunogold for visualization.

Results: mTG and gliadin were taken up and transported to the ER of NE and RACE cells. Overall, 7.5 ± 4.5 % (mean ± SD) of mTG and 6.8 ± 3.7 % (mean ± SD) of gliadin were localized in the ER of NE, thus exceeding the background label (BL) significantly (mTG BL: median: 1.0 % (IQR: 2.0), p < 0.0001; gliadin BL: median: 1.5 % (IQR: 3.8), p < 0.0001). When coincubated with mTG, gliadin localized to a higher extent in vacuoles, whereas its proportion in the cytosol was decreased (fig. 1A). Simultaneous incubation with FF diminished the transport of mTG into vacuoles, but increased its amount in the cytosol (fig.1B).

RACE cells of CD patients displayed an enhanced absolute uptake of gliadin into the ER, independent of the mode of incubation (gliadin in mTG/FF (CD) 7.7 ± 2.7 (mean ± SD); FF alone (CD) median: 7.5 (IQR: 6.3) vs gliadin in mTG/FF (NCD) median: 4.0 (IQR: 3.8); p < 0.001; p = 0.016), whereas transport of mTG into this compartment was dropped to the level of NCD patients in mTG/FF-incubated samples (mTG in mTG/FF (CD) median: 6.0 (IQR: 3.8) vs mTG alone (CD) median: 11.0 (IQR: 7.5); p < 0.001; mTG alone (NCD) median: 6.5 (IQR: 3.8)).

Conclusion: This study showed that mTG and gliadin are taken up and transported to the ER of...
enterocytes, a prerequisite for cross presentation. Simultaneous incubation with mTG led to a higher uptake of gliadin into vacuoles of NE, where exogenous antigen presentation is initiated, and into the ER of RACE cells. mTG localized stronger in the cytosol of NE and its amount in the ER of RACE cells decreased to the level of NCD patients in mTG/FF-incubated samples. Finally, RACE cells of CD patients contained more gliadin in the ER than RACE cells of controls.

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Gender differences in the manifestations of paediatric coeliac disease. A Swedish cohort of 1030 patients

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Objectives and Study: The Swedish "coeliac epidemic period" (1984–1996) is defined by one of the highest prevalences of the paediatric form of the disease in the world. The aim of this retrospective study was to assess the changing pattern of clinical features of coeliac disease among Swedish children over a 41-year period with special focus on possible gender differences.

Method: A total of 1030 paediatric patients were diagnosed with coeliac disease from 1973 to 2013. Available material from filed data included information on sex, age, and clinical symptoms at disease onset. The study period, for comparative purposes, was divided into three sub-periods (1973–1983, 1984–1996 and 1997–2013) named pre-epidemic, epidemic and post-epidemic. The frequency of patients with gastrointestinal symptoms, extra-intestinal symptoms, and failure to thrive and/or short stature at presentation was analyzed. The differences in sex, age and symptoms were analyzed using the chi² test and one-way ANOVA.

Results: The mean age at diagnosis increased significantly for both female and male patients during the post-epidemic period, but there were no significant differences concerning the mean age at diagnosis between the two sexes during any period. There were more female than male patients in all the three study periods. In recent years, the asymptomatic and monosymptomatic form of coeliac disease has been more common for both females and males (p<0.05). The frequency of female and male subjects with extra-intestinal symptoms and failure to thrive and/or short stature at presentation decreased during the years (p<0.05). No statistically significant difference was observed between the girls and boys with gastrointestinal symptoms during the whole study. Females suffered primarily from gastrointestinal symptoms and growth failure through all study periods. Males presented more often with gastrointestinal symptoms and growth failure at the first two study periods. No statistically significant difference was detected between the two sexes and the gastrointestinal symptoms, the extra-intestinal symptoms and growth failure when compared for each of the three study periods. Notably, males were more often detected by screening during the post-epidemic period than females (p=0.0096).

Conclusion: The change in the clinical pattern at paediatric coeliac disease onset seemed to follow a parallel path for both sexes during the past four decades in Sweden. The gastrointestinal symptoms were the most common debut symptoms in both sexes during the whole study period. The mean age at disease onset increased drastically in both sexes during the recent years. The female disease dominance remained unchanged during the years. During the last study period more males were detected through screening in comparison to females.

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Celiac disease, sleeping disorders and neurological symptoms: a prospective study in 47 children

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Objectives and Study: According to Oslo definition, coeliac disease (CD) is a systemic immune-mediated disorder. It is known that some celiac patients can be asymptomatic, but some show vague symptoms. During the past two decades, a growing body of neurological disorders has been reported in both adults and children. The wide spectrum of neurological conditions reported includes peripheral neuropathy, cerebellar ataxia, myelopathy, myopathy, brainstem encephalitis, epilepsy and headache. The aim of our study was to assess whether celiac children are at risk of electroencephalographic findings, headache and sleep disordered breathing, and whether an appropriate gluten free diet may influence these disorders.

Method: We consequently enrolled 47 children (age: 2-17 years) who received CD diagnosis. 19 children were enrolled between 2012-2013 and the other patients from 2015. All patients, at diagnosis, have undergone a general and neurological examination and an electroencephalogram. They filled in a questionnaire investigating neurological features as headache (diagnosed by International Classification of Headache disorders), migraine, epilepsy and a validated questionnaire assessing sleep disordered breathing (Sleep Clinical Record). The electroencephalogram was repeated only in patients who showed abnormal EEG findings at the first exam after 6 month and after 12 month of gluten free diet (GFD).

Results: 16/47 (34%) children reported abnormal EEG findings. After 6 months of GFD, EEG abnormalities disappeared in 7 children (43,75%); among the remaining 9 children, symptoms improved in 2, were unmodified in 4 children and 3 children didn't return to follow-up. After 12 months, 5/6 (83.3%) patients returned; EEG abnormalities worsened in 1 patient, improved in 2 children and disappeared in 2 patients. 24/47 (51%) children had headache at the moment of diagnosis. After 6 months of GFD, headache disappeared in 16, improved in 3 patients, and was unmodified in 2 patients; 3 children were lost at follow-up. After 12 months of GFD headache reappeared in 1 child and disappeared in 3 children. 18/47 (38,29%) children had Sleep Disordered Breathing (SDB) (6 children had snoring and in 1 of this apnea was present too). After 6 months of GFD, SDB improved in 3 patients and disappeared in 9; one patient was lost at follow-up. After 12 months, SDB reappeared in 1 child, disappeared in 4 children, improved in one patient and was unmodified in 3 children. For CD follow-up, after 12 months of GFD, anti-transglutaminase IgA titer was negative in all, except for 2 children.

Conclusion: In conclusion, our results suggest that gluten free diet may play a decisive role in presence of unexplained EEG abnormalities and in other neurological disorders as headache or sleep disordered breathing.

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Selective pancreatic amylase deficiency in children

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Objectives and Study: Dissociation in the intrauterine and postnatal expression of the three lines of pancreatic enzymes has been well established. Among pancreatic enzyme expression amylase occurs last. Based on previous studies no pancreatic amylase could be detected for the first two months after birth in duodenal aspirates from full-term and preterm infants. Isolated amylase deficiency has been described beyond infancy. The goal of this study was to assess the prevalence of isolated amylase deficiencies in children 0-18 years of age.

Methods: The database of over 800 endoscopic pancreatic function tests (ePFT) was searched for cases when the amylase activity was less than third percentile of normal and the other two enzyme groups (lipase and proteases) had normal activities.

Results: A total of 61 children between the ages 0.28 and 15.7 years (male, n=33; &LT;2 years =49) had isolated amylase deficiency and among them 15 had 2 or more ePFTs (n=79). The main indications for ePFT were failure to thrive (n=46), diarrhea (n=22) and nausea/vomiting (n=21). All except for 3 were born at term. There were 42 children whom were breast-fed and subsequently diagnosed with FTT. Interestingly, the most frequent endoscopic finding was allergic proctitis (n=31). Among the 15 patients who had repeat ePFT, 13 had normal ePFT and 2 had abnormal activity suggesting permanent deficiency. Repeat ePFT occur on average 1.41 years after initial ePFT. The initial amylase activity changed from 5.02 ±3.2 to 19.7±9.35.

Conclusions: Malabsorptive symptoms were associated with isolated amylase deficiency in 61 children. While it is generally accepted that low amylase activity is “physiologic” in infants &LT;6 months of age, 56 of the children were >6 months of age. The results of the repeat ePFTs suggests that maturational delay in amylase activity may occur beyond 6 months of age. Selective amylase deficiency should be considered in the differential diagnosis in children with FTT and diarrhea.

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Does the pancreas divisum reflect the clinical course of chronic pancreatitis in children?

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Objectives and Study: Chronic pancreatitis (CP) among children is a rare entity with a diverse etiology. Major risk factors of the disease include gene mutations, biliary diseases, lipid disorders and anatomical defects of pancreatic duct. The leading anomaly from the latter is pancreas divisum (PD), which role in etiology and clinical course of CP remains controversial. The aim of the study was to analyse the clinical presentation of CP associated with pancreas divisum (group 1) in comparison with CP related to other risk factors (group 2).

Method: A total of 327 patients with CP, hospitalized from 1988 to 2016 were enrolled into the study. Patients with mutation of PRSS1 gene were excluded. Medical records of children were reviewed for data on presentation, diagnostic findings and implemented treatment.

Results: Pancreas divisum was found in 34 (10.4%) children in investigated cohort. The median age of the disease onset was 9.2 in children with PD comparing to 9.8 years (NS) among the rest of CP patients. The mean number of episodes of pancreatitis was 5.5 vs. 4.0; p&LT; 0.05. Calcifications on imaging studies were found in 17 (50%) vs. 97 (33.1%) children; p&LT; 0.05. Thirty vs. 170 (88% vs. 58%; p&LT; 0.05) patients had ERCP performed, the mean number of procedures was 3.5 vs. 5.0; NS. The grade of inflammatory lesions assessed with Cambridge scale was comparable (median 2 vs. 2; NS). Sixteen children with PD had pancreatic sphincterotomy vs. 88 patients from compared group (47% vs. 30%, p&LT; 0.05). Pancreatic duct stenting was conducted in 20 children from group 1 vs. 72 children from group 2 (58.8% vs. 24.6%; p&LT; 0.05). The surgical treatment was undertaken in 3 vs. 14 patients (8.8% vs. 4.8%; p&LT; 0.05). In 4 children vs. 35 (11.8% vs. 11.9%; NS) exocrine insufficiency was diagnosed. No patient from the PD group was diagnosed with diabetes comparing to 18 children from the second investigated group (0% vs. 6.1%; p&LT; 0.05).

Conclusion: The CP associated with pancreas divisum in children characterize with more severe clinical course comparing to CP related to other risk factors. The exacerbations of pancreatitis were more frequent and endoscopic or surgical treatment were undertaken more often in patients with PD.

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Faecal microbiota profiles of healthy Hong Kong toddlers and explained variance by various subject parameters

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Objectives and Study: The gut microbiome is increasingly linked to a variety of health outcomes and recognised as (nutritional) target for maintenance or recovery of health. In contrast to the development of infant microbiome, there is little published data on faecal microbiota composition of healthy toddlers. Therefore, this study investigated faecal microbiota in a large group of toddlers.

Methods: Fresh faecal samples (stored at -80°C) were collected from 160 healthy toddlers, aged 1-2.5 years, of Chinese origin and living in Hong Kong. Subjects are a sub-cohort of a larger trial (registration identifier: NTR4779) and faecal samples were collected at study baseline. DNA was isolated by mechanical lysis and subsequent purification, followed by 16S rRNA gene Illumina sequencing. Potential links between microbiota composition and subject parameters were identified using multivariate approaches (principal component analysis and redundancy analysis) as well as univariate analysis (aimed at identifying individual taxa). Subject data were obtained from parents by structured interview including a food frequency questionnaire (suitable for Asian target group) to assess daily nutrient intake.

Results: Technical controls showed that quality of the sequencing data was sufficient and allowed downstream data analysis and interpretation. Microbial genera most abundantly found and together comprising >70% of total were (in decreasing order): Bifidobacterium, Blautia, Ruminococcus, Bacteroides, Collinsella and Streptococcus. Multivariate analysis showed a striking separation of samples into a low and high Collinsella group (“enterotype”), which was not explained by any of the investigated variables. Phylogenetic diversity in the Collinsella-rich group was significantly higher compared to the Collinsella-poor group. Microbiota composition was most strongly linked with age, explaining 2.1% of the total variation observed in microbiota composition. Older toddlers are associated with higher relative abundances of adult-like taxa such as Ruminococcus and Faecalibacterium. Daily nutrient intake accounted for 1% of the variation with strongest association with calories, carbohydrates and phosphorous. Having a sibling explained 0.7%. Only 0.5% of the variation in the faecal microbiome could be explained by stool consistency (Bristol stool score). Although significant, this was much less than reported from adult studies. Daycare attendance was responsible for 0.4%. Remarkably, breastfeeding duration from birth (none, < 2 months, >2 months) did not explain any variation in faecal microbiota composition of the toddlers.

Conclusion: The faecal microbiome of healthy toddlers is still dominated by Bifidobacterium as in infants, but the growing diversity reflects transition from infancy to adulthood. The variances explained by each of age, diet, breastfeeding, stool consistency and contact with age peers are below ~2%, which confirms that most variation lies among individuals and cannot be explained by the metadata available.

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Objectives and Study: While the extent necrotic changes within the ischemic intestine directly correlates with the duration of ischemia, we tested in the present study whether intestinal cell turnover (proliferation and apoptosis) are related to the time of reperfusion in a rat model of intestinal ischemia-reperfusion (IR).

Method: Male Sprague-Dawley rats were divided into 4 experimental groups: 1) Sham-24 rats underwent laparotomy and were sacrificed 24 hours later, 2) IR-24 rats underwent occlusion of both superior mesenteric artery and portal vein for 30 minutes followed by 24 hours of reperfusion, 3) Sham-48 rats underwent laparotomy and were sacrificed 48 hours later, 4) IR-48 rats underwent occlusion of SMA and SMV for 30 minutes followed by 48 hours of reperfusion. Intestinal structural changes, Park’s injury score, enterocyte proliferation and enterocyte apoptosis were determined 24 hours or 48 hours following IR. The expression of Bax, Bcl-2, p-ERK and caspase-3 in the intestinal mucosa was determined using real time PCR, Western blot and immunohistochemistry.

Results: 24 hours following intestinal ischemia, IR rats demonstrated a strong increase in Park injury score (2.5-fold increase in jejunum and 3.5 fold increase in ileum) compared to sham-24 rats that was accompanied by a strong decrease in cell proliferation (33% in jejunum and 24% in ileum) and increased cell apoptosis (5-fold increase in jejunum and 3-fold increase in ileum). 48 hours following intestinal ischemia, IR rats demonstrated a less significant increase in Park injury score (2-fold increase in jejunum and 2.5 fold increase in ileum) as well as less significant decrease in cell proliferation and less significant increased cell apoptosis compared to Sham-48 animals. IR-48 rats demonstrated a greater levels cell proliferation and lower rates of cell apoptosis compared to IR-24 hours. Elevated cell apoptosis was accompanied by a significant increase in Bax/Bcl-2 ratio (gene and protein levels).

Conclusion: Intestinal reperfusion as well as ischemia results in a most significant damage within 24 hours following IR insult. 48 hours after IR, rats demonstrate signs of intestinal recovery.

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Milk feeding prevents gut bacterial translocation but not responses to systemic infection in preterm pigs

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Objectives and Study: Bloodstream infection (BSI) is the most frequent severe complication afflicting preterm infants and often results from either prolonged use of indwelling catheters or gut microbial translocation. Breastfeeding preterm infants protects against BSI and sepsis, but it is unclear whether the effect is direct (systemic delivery of milk-derived antimicrobial factors) or indirect (improvement of gut integrity). We hypothesized that enteral feeding of preterm neonates diet-dependently affects both gut- and catheter-derived bacteremia. Hence, we compared the protective effects of milk and formula feeding against BSI.

Method: Preterm, cesarean-delivered pigs were fed either bovine colostrum (MILK) or infant formula (FORM). On day 3, animals received 5*10⁹ CFU/kg intravascular Staphylococcus epidermidis (SE) (SE-MILK, n=8; SE-FORM, n=8) or control saline (SAL-MILK, n=4; SAL-FORM, n=7). On day 5, clinical status, organ pathology, bacteriology and hematological parameters were assessed.

Results: Fewer milk-fed animals had gut lesions (9 vs. 80%, p< 0.001) and translocation of enteric bacteria (Enterococcus spp.) to the bone-marrow (33 vs. 80%, p< 0.05) compared with formula-fed counterparts irrespective of SE status. SE-infected animals were not clinically affected despite high densities of SE in blood and bone marrow, as well as markedly reduced circulating platelets and lymphocytes (both p< 0.01) compared with controls. SE infected animals also showed increased ex vivo blood neutrophil phagocytic function, indicating improved innate immune competence. Milk feeding did not alter neutrophil function nor improve SE clearance in vivo.

Conclusion: Milk feeding prevents gut inflammation and bacterial translocation compared with infant formula, but does not prevent catheter-induced BSI. In preterm infants, the beneficial effects of milk feeding on BSI may be mostly related to improvement of gut barrier integrity.
[Pathology, hematology and microbiology measurements after SE-infection and milk vs. formula feeding]

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Features of species composition of Bifidobacterium and intestinal microbial profile in children in first half of life

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Objectives and Study: Quantitative and qualitative violations of microbial composition and range of SCFA on the first year of life, related with the way of delivery (cesarean section), unreasonable using of antibiotic therapy, have long-term negative effects with higher risk of development of allergic diseases, obesity, first-type diabetes and etc. Changes of SCFA's range in feces can show qualitative condition of intestinal microbiocenosis in children and can be used for screening evaluation it’s status. The aim of the study was to juxtapose parameters of microbial metabolism in infants with intestinal microbiological features and species composition of bifidobacteria in intestines.

Method: Examined 91 children in the age of 4-6 months before introducing comlimentary foods. Of them there were 57 breast-fed children and 34 children on artificial feeding. Clinical manifestations of functional digestive violations with moderate severity (regurgitation, rumination, colics, constipation, infant disease) were detected in 75 children (82.4%) For all were made study of intestinal microbiocenosis through bacteriologic research, PCR diagnostics. Examination of content SCFA fractions C2-C6 in feces: acetic, propionic, butyric, valeric, nylon, was made, using method of gas-liquid chromatographic analysis.

Results: Established, that natural born children, unlike cesarean section born children, had significantly higher average content of acetic acid.(1,59±0,75 и 1,04±0,56, p&LT; 0,05) Anaerobic index in cesarean section born children was declined in negative way, than in natural born children (-0,23±0,14 и -0,16±0,13, p>0,05). The most expressed changes of SCFA, characterized increasing of acetic content, decreasing of propionic, and butyric acids, significant increasing of isoacids level, were identified only in children with intestinal dysbiosis III degree, and never met in I and II degrees of dysbiosis. (0%, 0%, 13,9%, p&LT; 0,05). Infant strains of bifidobacteria in feces were typed only in 40% of children with the mostly expressed changes of SCFA range unlike children with less expressed changes of SCFA, under which infant strains were detected in all children (p&LT; 0,05).

Conclusion: Were shown features of SCFA range in feces and more pronounced dysbiotic changes in intestines in cesarean born infants. Indicators of SCFA range, typing, and lack of infant strains of bifidobacteria can be used for diagnostic purpose in pediatric practice for assessing the degree of dysbiosis. Dynamic research of range and types of SCFA composition in faces in children can be diagnostic and prognostic criterion of effectiveness of conducted therapy, that takes further studies.
Impact of early life nutrition on gut function and resilience in later life

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²Nutricia Research, Utrecht, Netherlands

Objectives and Study: The first thousand days of life are a critical time of development in humans, and can modify the risk profile for diseases in later life. However, the long-term consequences of the early environment on the susceptibility to intestinal disorders have not yet been assessed. The aim of the present study was to investigate the impact of the early nutritional environment on intestinal maturation and gut function and resilience in later life, using a mouse model of postnatal growth restriction (PNGR).

Method: PNGR was induced in FVB/NRj mice during the suckling period by adjusting the litter size to 15 pups per mother. We investigated the impact of PNGR on intestinal maturation and gut colonization in pups at weaning, and on severity of chronic chemically induced-colitis in adulthood.

Results: PNGR was associated with an alteration of the intestinal barrier in pups at weaning, characterized by an increased intestinal permeability and impaired tight junctions. At the same time, the expression of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 was increased in the colon in pups with PNGR. PNGR affected gut bacterial colonization, with decreased bacterial diversity, higher Enterococcus spp, Staphylococcus spp, and Escherichia-Shigella spp, and lower Odoribacter spp and several members of the Lachnospiraceae family in pups at weaning. The lack of an efficient intestinal barrier and the dysbiosis induced by PNGR in early life were associated with a pro-inflammatory colonic status and a higher susceptibility to chronic chemically induced-colitis in later life.

Conclusion: Our data emphasize the influence of the early nutritional environment in programming of gut health in later life, and support the hypothesis of the developmental origin of chronic intestinal disorders. Further studies are necessary to identify the underlying mechanisms.

Disclosure of interest: The present work is a collaborative research between Lille Inflammation Research International Center and Danone Nutricia Research.

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Gut microbiome in newborns affected by intestinal ischemic lesions. Preliminary report

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Objectives and Study: Early life microbiota plays a crucial role in human health by acting as a barrier from pathogens invasion and maintaining the intestinal immune homeostasis. Reduced bacterial diversity and altered microbiota composition have been found in newborn affected by bowel ischemic and inflammatory injuries such as necrotizing enterocolitis (NEC). The aim was to identify changes in intestinal microbiota and mucosal lymphocytes in newborn with intestinal ischemic lesions.

Method: From September 2016 to July 2017, 16 intestinal full thickness specimens were obtained from 14 newborns underwent to intestinal resection because of bowel ischemia (Table 1). Two groups were identified: focal ischemia (FI) and extended ischemia (EI). For each group we determined the mucosal (M), fecal (F) and enteral washing (EW) microbiota profiling through targeted metagenomics followed by a- and b-diversity index assignment of microbial ecology and Kluskal-Wallis analyses of Operational taxonomic units (OTUs) at Phylum and Species levels. Cytofluorimetry was performed on intestinal tissue to phenotype and analyze mucosal T lymphocytes.

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>&lt;30 weeks GA</td>
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<td>8</td>
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<tr>
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<td>NEC</td>
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<tr>
<td><strong>Focal Ischemia</strong></td>
<td></td>
</tr>
<tr>
<td>Isolated intestinal perforation</td>
<td>4</td>
</tr>
<tr>
<td>Intestinal Atresia</td>
<td>3</td>
</tr>
<tr>
<td>Colonic stenosis</td>
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</table>

[Table 1. Clinical features of the patients]

Results: The M, F and EW microbial community compositions varied between the two groups, showing in EI profile the predominance of Proteobacteria and Enterobacteriaceae. Specifically, in group EI the M microbiota was characterized by higher Shannon index and lower Chao I index, the Phylum level classification showed a significant prevalence of Proteobacteria and reduction of Bacteroidetes and Verrucomicrobia and the Enterobacteriaceae was the most abundant taxonomic family. The species analysis showed a significant difference (p< 0.05) between the two groups characterized by a reduction of Bacteroides, Lachnospiraceae and Ruminococcaceae in EI. No significant differences in T cells population (Treg, Th17, CD4 and CD8) were observed at the cytometric analysis of intestinal samples in each group. The Tumor necrosis factor- α (TNFα) production was significantly difference (p< 0.05) between the two groups: EI showed higher level of TNFα.

Conclusion: Our results suggest the relevance of specific microbiota signatures in neonatal bowel ischemic events. Microbiota diversity and specific species, such as Enterobacteriaceae, may be crucial in determining and maintaining the grade of inflammation and promoting the ischemia extension. The scale up of sampling is currently in progress to transform microbiota signatures into microbial EI markers.

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Mycophenolate mofetil (MMF) and tacrolimus (Tac) synergistically inhibit proliferation of colonic adenocarcinoma cell line and might impede colorectal tumorigenesis

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Objectives: Immunosuppressive treatment is associated with increased risk of development of cancer and should be avoided in patients with neoplasia or pre-neoplastic conditions. Recently, we have observed complete reversion of familial adenomatous polyposis (FAP) phenotype in a FAP patient treated with tacrolimus (Tac) and mycophenolate mofetil (MMF) following kidney transplantation1. The aim of the study was to assess the ability of MMF and Tac to inhibit proliferation of colonic adenocarcinoma cell line HT29.

Methods: HT29 cells were cultured in DMEM medium supplemented with 10% fetal calf serum, L-glutamine and antibiotics. Cells were treated with 0.1 or 1 µM Tac, 1 or 10 µg/ml MMF and with combinations of Tac and MMF (0.1 µM and 1 µg/ml, 1 µM and 10 µg/mL, 0.1 µM and 1 µg/ml, 1 µM and 1 µg/ml, respectively). Control cells were treated with vehicle alone. Cell proliferation was assessed at 24, 48, 72 and 96 hours using MTT assay and results were expressed as percent of control at the same time point. Cell cycle was assessed using propidium iodide staining and flow cytometry following 96 hours or treatment.

Results: Treatment of HT29 cells with combination of 1 µg/mL MMF and 0.1 or 1 µM Tac resulted in significant inhibition of proliferation at 48, 72 and 96 hours (82.9±11.46%, 48.37±8.1%, 86.06±25.45%, or 81.1±13.6%, 73.4±10.4%, 89.2±20.6%, respectively, p< 0.001, compared to control). Elevation of Tac concentration did not have additive effect. Significant impediment of growth of HT29 cells was also observed following 72 and 96 hours of treatment with 10 µg/mL MMF alone (56.26±22.26%, 76.13±20.12%, respectively, p< 0.002, compared to control) or in combination with 1 µM Tac (56.9±20.89%, 76.4±24.47%, respectively, p< 0.001, compared to control), whereas addition or 0.1 µM Tac to 10 µg/ml MMF resulted in sustained inhibition of proliferation of HT29 cells at 24, 48, 72 and 96 hours (82.5±11.7%, 58.5±11.3%, 56.91±20.89%, 54.82±8.73%, respectively, p< 0.004, compared to control). Tac alone in both concentrations and MMF alone in concentration of 1 µg/ml did not influence proliferation of HT29 cells (Fig. 1). The observed cytotoxic effects were characterized by concomitant G1-S phase arrest.
**Discussion:** Our results demonstrate synergistic inhibitory effect of MMF and Tac on proliferation of colonic adenocarcinoma cell line HT29 and confirm our clinical observation. Colonic adenocarcinoma cells are endowed with intrinsic mechanism of resistance to MMF treatment, namely glucuronidation of the latter\(^2\). The ability of Tac to inhibit this process\(^3\), thus improving the bioavailability of MMF, might provide mechanistic explanation of our findings. Further studies, aimed at elucidation of additional molecular mechanisms explaining the observed phenomena are underway. Our results point to a possibility of novel approach to therapy of colorectal neoplasia based on the use of MMF analogues resistant to glucuronidation.

**References:**

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Efficacy and safety of gelatine tannate for the treatment of acute gastroenteritis in children: a randomised controlled trial

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Objectives and Study: Recently, in many European countries, gelatine tannate is being widely marketed for treating acute gastroenteritis. Gelatine tannate is a complex of tannic acid, which possesses astringent and anti-inflammatory properties, and a protective gelatine. The objective of this study was to assess the efficacy of gelatine tannate for the treatment of acute gastroenteritis in children.

Method: This was a double-blind, placebo-controlled, randomised trial. Children younger than 5 years of age with acute gastroenteritis defined as a change in stool consistency to loose or liquid form (according to the Bristol Stool Form scale or Amsterdam Stool Form scale) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24 h), lasting for no longer than 5 days, were recruited. 72 children were assigned to receive gelatine tannate (n=36) or placebo (n=36) in addition to standard rehydration therapy. The gelatine tannate was administered at an age-dependent dose (250 to 500 mg), and both study products were taken 4 times/day for 5 days.

Results: Sixty-four children (89%) completed the intervention and were included in the analysis. The duration of diarrhea after randomization was similar in the gelatine tannate and placebo groups (75.6 ± 27.8 versus 75.5 ± 29.0 h, respectively, mean difference 0.1 h, 95% CI -14.1 to 14.3 h). There was no significant difference between groups in the number of watery stools per day throughout the study period. There were also no differences in any other secondary outcome measures between groups.

Conclusion: In children with AGE younger than 5 years of age, gelatin tannate was ineffective as an adjunct to rehydration therapy.

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Objectives and Study: According to the Global Health Observatory, childhood obesity has been increasing worldwide. One of the most concerning comorbidities is insulin resistance (IR), which can lead to type 2 diabetes and increase cardiovascular risk. There are several methods to assess IR. In this study we compare single blood sample methods and, the influence of obesity during paediatric years in insulin resistance and its clinical effects.

Method: A transversal and observational study was conducted concerning patients observed in the obesity appointment of Paediatric Gastroenterology and Nutrition Unit from a tertiary Hospital, between 1st February 1999 and 1st May 2017, with the data collected from the prospective hospital’s clinical database. Initially, single blood sample methods to evaluate IR - fasting insulin, C peptide, HbA1C, HOMA-IR and QUICKI - were compared. Then, the sample was separated based in IR assessed by HOMA-IR, and compared to analytical and physical exam parameters.

Results: Were included 1496 children, 862 with overweight (57.6%) and 634 with obesity (42.4%). Significant Pearson correlations were found between the methods to assess IR evaluated - between fasting insulin and C peptide ($r(1045)=.704, p<.001$), HOMA-IR ($r(1085)=.984, p<.001$) and QUICKI ($r(1085)=-0.800, p<.001$). C peptide with HOMA-IR ($r(1029)=.712, p<.001$) and QUICKI ($r(1029)=-.661, p<.001$) and between HOMA-IR and QUICKI ($r(1085)=-.803, p<.001$) - except for HbA1C which showed none statistically significant correlations. Using HOMA-IR to assess IR, statistically significant results were found when comparing HDL ($t(1077)=5.87, p<.001, d=0.40$) between both groups, with lower values in the IR group ($M=49.82, SD=11.96$) versus the non-insulin resistant (NIR) ($M=45.29, SD=10.68$). Concerning LDL, ($t(1064)=2.40, p=.017, d=0.16$), significant results were found as well, with a mean in the NIR group of 99.16 ($SD=28.25$) and in the IR one of 94.65 ($SD=27.81$). Triglycerides ($t(1072)=7.96, p<.001, d=0.50$), showed statically significant higher values in the IR group ($M=105.47, SD=55.37$) against the NIR ($M=80.80, SD=42.05$). Fasting glucose ($t(1086)=10.58, p<.001, d=0.65$) also revealed a higher mean ($M=89.33, SD=7.07$) in the IR group, comparing to the NIR one ($M=83.70, SD=7.07$). Acanthosis ($\chi^2=35.68, p<.001, \phi =.19$) showed a higher percentage in IR children (63.3%), comparing to the NIR ones (42.9%), and the same happened with hepatic steatosis ($\chi^2=19.25, p<.001, \phi =.18$), that showed a percentage of 16.0% in the NIR group and 68.0% in the IR one. Concerning total cholesterol ($t(1081)=1.70, p=.090, d=0.11$), hsPCR ($t(143)=1.54, p=.124, d=0.15$), systolic ($t(1084)=1.23, p=.219, d=0.09$) and diastolic ($t(1084)=1.69, p=.091, d=0.12$) arterial tension, and abdominal perimeter ($t(1037)=0.67, p=.502, d=0.04$), no significant results were found.

Conclusion: The single blood sample methods - fasting insulin, C peptide, HOMA-IR, QUICKI - were concordant and equally good assessing insulin resistance. From the relationship observed between childhood obesity and insulin resistance, we verified that insulin resistance had a significant association with acantheosis nigricans, hepatic steatosis, decrease HDL, increase triglycerides, pointing to an increasing risk of development of type 2 diabetes and cardiovascular diseases.

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Infantile-onset Colitis resulting from RTEL1 mutation

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Objective: Wide use of sequencing platforms in patients with extreme inflammatory bowel disease (IBD) phenotypes have lead to discovery of more than 50 monogenic disorders. For selected patients, identifying the specific mutation can have major implications on treatment, monitoring and outcomes. We report on a young patient with infantile-onset colitis who was found to have a deleterious mutation in regulator of telomere elongation helicase 1 (RTEL1) gene.

Methods: A 12-month-old Ashkenazi Jew female from a non-consanguineous family was evaluated for bloody diarrhea that developed at the age of 10 months, without history of significant infections. Treatment with steroids was commenced following endoscopic evaluation that showed pancolitis, but was ineffective. Detailed immune and genetic work was performed and telomere length was evaluated by in-gel hybridization assay.

Results: Although the patient had normal immunoglobulin levels, the frequency of B cells in the blood was extremely low. Through whole exome sequencing we identified an autosomal recessive deleterious C.3791G>A missense mutation in RTEL1. Sanger sequencing confirmed that the parents are carriers and the proband is homozygote for this variant, which is common among Ashkenazi Jews. In-gel hybridization assay showed that patient's telomeres are shortened in comparison with her parents. Brain MRI demonstrated cerebellar atrophy. Based on these findings, that patient was diagnosed with Hoyeraal-Hreidarsson syndrome.

Conclusions: Patients with RTEL1 mutations can develop isolated colitis, without overt immunodeficiency features. Given the relatively high carrier frequency of the C.3791G>A variant in the Ashkenazi Jewish population, a high index of suspicion should be raised in Israeli very early-onset IBD patients.

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Application of molecular methods for evaluation of a case of suspected macro-aspartate aminotransferase

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Objectives and Study: Macro-aspartate aminotransferase (macroAST) in the circulation is formed by combining with immunoglobulin (Ig), resulting in a high molecular weight form of AST. AST values are persistently increased as a consequence of reduced inactivation, clearance or excretion which rises problems with the clinical interpretation of an abnormal AST activity. We have recently reported a monogenic defect responsible for macro AST, which detection can be employed by clinicians (J Hepatology 2017). The aim of the study was show the possible clinical application of molecular analysis to diagnose macroAST due to the mutations identified in GOT1 gene.

Method: A healthy 13 year-old male was referred because of chronic elevated AST (116 U/L) and low IgG levels (6 g/l) without other abnormalities. Macro-AST positivity was suspected based on enzyme precipitation activity which was 56% (borderline result) but in the electrophoretic study with depletion IgG, we did not confirm the presence of macroAST. To clarify the diagnosis we used whole exome sequencing (WES)-based analysis.

Results: A missense variant (p.Gln208Glu, rs374966349) in glutamate oxaloacetate transaminase 1 (GOT1) was found, as a putative causal variant predisposing to familial macro-AST. In silico analysis demonstrated that the amino acid at this position is not conserved among different species and that, functionally, a negatively charged glutamate on the GOT1 surface could strongly anchor serum immunoglobulins.

Conclusion: Preliminary data highlight that testing for the p.Gln208Glu genetic variant may be useful in diagnosis of macro-AST and could be used beside or complementary to precipitation and electrophoresis tests. The IgG method was straightforward and provided unambiguous results. However, given the affinity of IgA and IgG, it likely only detects AST-IgG macrocomplexes.

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Is the low-grade enteropathy coeliac disease in the pediatric age?

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Objectives and Study: The 2012 ESPGHAN criteria for the diagnosis of coeliac disease (CD) acknowledged that the natural history of low grade enteropathy (Marsh 1) is poorly understood, and therefore the need for a gluten free diet (GFD) in these subjects is an important area of uncertainty. In the absence of guidelines, this type of lesions has become a challenge for clinicians and there are not clear rules about the management of this pathology. The aim of our study is to assess the characteristics of patients with Marsh 1 in the Spanish National Registry of Coeliac Disease (REPAC2) from January 2011 to September 2016.

Method: A retrospective review was performed in the REPAC2 register. We contacted the Paediatric Gastroenterologists from those centers who had patients with Marsh 1 lesion to check that the histological diagnosis was correctly registered. We asked them whether a GFD was recommended and if so, the clinical and serological response to the gluten withdrawal was assessed. If a gluten challenge was performed later they were asked about the clinical, serological and histological response. Demographic, clinical, serological and histological variables included in REPAC 2 were analyzed. In the centers with Marsh 1 patients a comparison was performed between them and the celiac patients diagnosed of Marsh 2-3 in the same period of time, to assess differences according to the variables analyzed.

Results: 71 out of 1733 children (4.09%) with intestinal biopsies were diagnosed as Marsh 1. Symptoms disappeared when gluten was removed from the diet and the antibodies were normalized after gluten free diet in all patients. However, only in 13 out of 71 the gluten challenge was carried out lately. In those cases symptoms related to gluten intake reappeared and antibodies were positivized. Only in 2 out of 13 patients endoscopic procedure was repeated with histological confirmation of CD. At the time of diagnosis mean age was 70 months (RIC 36-100) and 65% were female. A total of 56 patients had symptoms (79%), the more often were abdominal pain in 49% (27/56), diarrhea in 32% (18/56), weight loss in 30% (17/56), and refusal feeding in 25% (14/56). The immunoglobulin A (IgA) anti-tissue transglutaminase antibodies (IgA-tTG) were ≥ 10 in 49 (69%) and < 10 in 21 (30%), weight loss in 30% (17/56) and refusal feeding in 25% (14/56). The immunoglobulin A (IgA) anti-tissue transglutaminase antibodies (IgA-tTG) were 1-9 times above normal level in 21 (30%) and ≥ 10 in 49 (69%). Median increase in the level of IgA-tTG / cut off value was 66 (RIC 29.4-119). Genetic study was performed in 62 patients of which 82% were HLA-DQ2 positive. The comparison between Marsh 1 and Marsh 2-3 patients showed that there were only significant differences in some variables. Marsh 1 had a greater number of relatives with CD (p = 0.015) and more diagnosis by screening (p = 0.05), but less abdominal distention (p &LT; 0.05). The median level of IgA-tTG antibodies and the increase above the cutoff value were significantly lower (p &LT; 0.001) than in the Marsh 2-3 groups.

Conclusion: This study contributes to the characterization of patients with suspected CD and low grade enteropathy, scarcely reported in the literature. Although we are aware of the limitations of this study, because of the small difference in most of the clinical variables between Marsh 1 and Marsh 2-3 children group we can speculate on the role of the low grade lesion at diagnosis of CD.

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HLA types and Coeliac disease in children: Any association in symptoms, biochemical and endoscopic findings?

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Objectives & Study: Genetic predisposition plays a significant role in Coeliac disease (CD) and it depends largely on the effect of specific HLA class II genes: HLA-DQ2 and HLA-DQ8. These genes regulate the adaptive immune response to gluten peptides and influence both innate and adaptive immune reactions, intestinal permeability and autoimmunity. Thus, disease presentation and findings may vary according to carried HLA-DQ alleles, however data is scarce. The aim of the study is to evaluate the relation between the disease characteristics and specific HLA-DQ alleles.

Methods: In this cross-sectional study, biopsy proven CD cases with HLA typing were recruited. According to HLA tests patients were divided into four groups: Only HLA-DQ2.2 positive (Group 1), only HLA-DQ2.5 positive (Group 2), only HLA-DQ8 positive (Group 3), both HLA-DQ 2.5 and HLA-DQ8 positive (Group 4). Demographic data, symptoms, biochemistry (haemoglobin (Hb), ferritin, vitamins), anti-tissue transglutaminase (TTG) IgA level and endoscopic findings were recorded. Patients with insufficient data, selective IgA syndrome and other accompanying systemic disease were excluded.

Results: Among 246 CD patients, 148 cases (mean age: 7.7±4.4 years, 56% girls) were eligible for the study. Demographic and biochemical data is shown in table 1. Diarrhoea was more frequent at presentation in group 1 (57.1%, 35.3%, 11.1%, 11.8% respectively, p< 0.01) but other symptoms were equally distributed. Endoscopic findings, lymphocytic gastritis, Helicobacter pylori infection rate and Marsh stage was indifferent among groups.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=14, 9.5%)</th>
<th>Group 2 (n=99, 66.9%)</th>
<th>Group 3 (n=18, 12.1%)</th>
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<td>187.2±53.3</td>
<td>196.8±64.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Folic acid (ng/mL, mean±SD)</td>
<td>7.1±3.8</td>
<td>6.4±4.3</td>
<td>8.1±1.5</td>
<td>6.7±6.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Vitamin D (IU/mL, mean±SD)</td>
<td>16.2±13.2</td>
<td>16.8±8.5</td>
<td>18.8±5.1</td>
<td>14±8.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anti-TTG IgA (U/mL, mean±SD)</td>
<td>248.8±70.4</td>
<td>203.7±88.2</td>
<td>248.1±100.1</td>
<td>154.9±87.2</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Conclusion: Our cohort suggests that, patients carrying both HLA-DQ2.5 and HLA-DQ8 alleles are characterized by older age at diagnosis and lower anti-TTG IgA levels. Besides, nutritional status of only HLA-DQ2.5 carriers is worse than others and we found that diarrhoea is more frequent in patients carrying only HLA-DQ2.2. HLA-DQ2.5 is the most frequent allele found worldwide as well as our study.

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**Objectives and Study:** Recently, it has become apparent that the prevalence of coeliac disease (CD) in Saudi Arabia (1.5%) is greater than that found in most of the European countries (1%). This has raised the question, is the Saudi population genetically susceptible to develop CD? Also, it is not clear what degree of risk is conferred by the HLA-DQ genotypes in the Arab ethnic population of Saudi Arabia as compared to Caucasians. In this study, we aimed to determine frequency of CD-predisposing HLA-DQ genotypes among Saudi population and sought to establish a CD-risk gradient associated with the HLA-DQ genotypes. In addition, the design of our study allowed us to compare HLA-DQ genotypes between symptomatic CD patients and CD children diagnosed during a recent mass screening study.

**Methods:** We recruited three groups: group I, 46 CD children diagnosed consecutively over the past 10 years; group II, 192 healthy controls matched with group I for sex, age and geographic origin; group III: 55 CD children diagnosed during the mass screening among schoolchildren. All of the participants were typed for \textit{DQ}A1 and \textit{DQ}B1 genes by polymerase chain reaction sequence specific oligonucleotide probes.

**Results:** Comparing group I to II, we identified 5 groups of CD-risk gradient: 1) very high risk associated with \textit{DQ}2.5/\textit{DQ}8 genotype [Odds ratio (OR) = 69, P-value &LT; 0.001]; 2) high risk associated with homozygous \textit{DQ}2.5 and \textit{DQ}2.5/\textit{DQ}2.2 genotypes [OR = 4.56, P-value = 0.012; OR=4.28, P-value = 0.003, respectively]; 3) intermediate-risk associated with \textit{DQ}8/\textit{DQ}2.2 (OR = 2.5), heterozygous \textit{DQ}2.5 (OR = 1.8), and homozygous \textit{DQ}8 (OR = 1.6); 4) low risk associated with homozygous \textit{DQ}2.2 (OR = 0.3), heterozygous \textit{DQ}2.2 (OR = 0.11), and heterozygous \textit{DQ}8 (OR = 0.11), and 5) very low risk associated with \textit{DQ}X.5 (OR = 0.08) and \textit{DQ}X.x (OR = 0.04). Comparing the groups III and I, we found a significant increase of heterozygous \textit{DQ}8 in group III (12.7% versus 2.2%; p-value = 0.045). Only one “silent” coeliac case in group III carries \textit{DQ}X.x but none in group I. Forty three percent of the healthy controls are at high risk (homozygous \textit{DQ}2.5 and \textit{DQ}2.5/\textit{DQ}2.2 in 8%) or intermediate risk (\textit{DQ}8/\textit{DQ}2.2, heterozygous \textit{DQ}2.5, and homozygous \textit{DQ}8 in 36%) to develop CD.

**Conclusion:** Saudi population is at 43% risk to develop CD, which might explain the high prevalence of CD in the Saudi community. The highest risk to develop CD in Saudi Arabia is associated with \textit{DQ}2.5/\textit{DQ}8 genotype followed by homozygous \textit{DQ}2.5 and \textit{DQ}2.5/\textit{DQ}2.2 genotypes. Heterozygous \textit{DQ}8 genotype is associated with intermediate risk for development of “silent” screening-identified CD but very low risk for development of symptomatic CD.

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Liver involvement in children with coeliac disease: experience of a big tertiary centre in eastern Turkey

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Objectives and Study: Liver abnormalities in coeliac disease are common. The aim of this study was to investigate the ratio of the children with coeliac disease followed in our clinic presenting with elevated aminotransferases.

Method: In this study, 519 paediatric patients with coeliac disease were retrospectively analysed and whose had elevated aminotransferase levels before the diagnosis of coeliac disease, were assessed.

Results: Elevation of aminotransferase levels were obtained in 66 (12.7%) patients among the 519 patients during the diagnosis of coeliac disease. Median age of these patients were 7.33±3.96 years (min 2, max 17 years). All of the patients had mildly elevation of aminotransferase levels except for one patient. Her aminotransferase levels were higher than ten times of normal, because of the chronic liver disease due to coeliac disease. Very mildly increase of the aminotransferase levels (40-50 U/l) were detected in 50% of the patients. Patients' liver function tests were reverted to normal except the two patients with chronic liver disease after six months of the gluten-free diet.

Conclusion: Coeliac disease should be investigated in patients with very mildly elevated aminotransferase levels.
Intracellular T-cell receptors in intestinal enterocytes in coeliac disease patients and controls - clinical characteristics

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Objectives and Study: Coeliac disease is an immunologic disorder of the intestine. After gluten exposure genetically predisposed persons show intestinal inflammation. In the past beside Gliadine also T-Lymphocyte receptors CD8, α/β-TCR and γ/δ-TCR in vacuoles and in the Golgi-apparatus of intestinal enterocytes could be shown. In our study intestinal biopsies of healthy subjects and coeliac disease patients were examined for the distribution of δ-TCR, Gliadine and non-classical MHC-I molecule CD1d in enterocytes along with other clinical parameters.

Methods: Intestinal biopsies of coeliac disease patients and controls were examined by Immunofluorescence microscopy. Antibodies for δ-TCR (TCS1), Gliadine (WB6/8) and CD1d (CD1d27.1) were used. Clinical, laboratory and histological data was collected.

Results: In 43% (n=42) of the samples δ-TCR was found in the apical membrane and the Golgi-apparatus of the enterocytes. All WB 8 positive samples (n=21) were δ-TCR positive as were the CD1d positive samples (n=35). 39% (n=22) of the coeliac disease samples tested positive for δ-TCR. No healthy controls were positive for δ-TCR. Three coeliac disease patients were under glutenfree diet, two of these were δ-TCR negative.

For the other parameters of body length, weight, BMI, positive family history for coeliac disease, coeliac disease antibodies and histology there was no significant difference for δ-TCR positive and negative patients.

Conclusion: Parallel exposures of CD1d and δ-TCR in enterocytes point towards a MHC-I dependent disease mechanism.

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Objectives and Study: Our group carried out the first Spanish cross-cultural adaptation of a specific coeliac disease (CD) questionnaire for children aged 8-18 called CDDUX. The purpose of this study is to develop a cross-cultural adaptation of the new disease-specific, Health Related Quality of Life Questionnaire (HRQOL) elaborated in USA (CDPQOL) for its use with Spanish celiac children aged 8-18 and to assess the validity and reliability of the CDPQOL Spanish version.

Method: This is a cross-sectional study about the quality of life of celiac children from 8-18 years using a specific HRQOL questionnaire (CDPQOL). This questionnaire explores various aspects related to living with CD and consists of 2 versions, one for children aged 8-12 with 13 items and another for children aged 13-18 with 17 items. The authors of this questionnaire were contacted to request permission for their use. This cross-cultural Spanish adaptation was performed according to the revised international guidelines. These include the translation by expert linguists, cognitive interviews with children of different ages, gender and socioeconomic status to analyze cultural adequacy. As well as the comparison of the Spanish with the original versions to establish semantic equivalence which allows us to obtain the definitive version in Spanish language. All the coeliac children invited to participate in the study were outpatients aged 8-18 with CD who attended the Gastroenterology Paediatric Units of two different hospitals. We included data of the first 6 months of the study. The psychometric properties were analyzed using the Cronbach’s alpha coefficient. Demographic and clinical variables associated with HRQOL were also assessed.

Results: The questionnaire was answered by 80 children of which 48 were girls (60%). The mean age was 11 (2-18). They lived with both parents in 67.5% of cases. The economic situation was good in 36.3%, normal in 37.5% and poor in 3.8%. In 60% of cases they did not have problems buying the gluten free products. The clinical presentation at onset according to Oslo criteria were: Classical CD in 65.3% and non-classical in CD 28%. They had a positive family history 4.2%, and associated diseases in 2.8%. When asked about the diet 97.3% affirmed a complete adherence, 86% had no difficulties in following the diet however 10% expressed difficulties when they went out to eat. Symptoms with transgressions were present in 30%. Cronbach’s α coefficient for the total score for children aged 8-12 was 0.824, and for children aged 13-18 was 0.867.

Conclusion: The Spanish version of CDPQOL questionnaire can be considered as a reliable measurement instrument of HRQOL for Spanish coeliac children.

Study partially financed by Fondo de Investigación Sanitaria (Spain) grant number PI16/00358

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GASTROENTEROLOGY - Coeliac disease

G-P-019

Gall bladder dysfunction in children with celiac disease

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Objectives and Study: Malabsorption is associated with altered GI and Gall Bladder Motility due to several mechanisms. The status of gall bladder function in children with untreated celiac disease is largely unexplored. This study assessed Gall Bladder Ejection Fraction (GBEF) in children with Celiac Disease (CD) prospectively; at baseline and after a period of Gluten Free Diet for 6 months, by ultrasonogram and hepatobiliary scintigraphy.

Method: This was a prospective study cleared by the Institute Ethics Committee. Fifty children with newly diagnosed CD fulfilling ESPGHN criteria 2012, aged between 5-15 years were enrolled after obtaining informed consent. All underwent gall bladder function evaluation at baseline before starting GFD, by ultrasound (post prandial change in volume and wall thickness), as well as by cholescintigraphy ($^{99m}$Technitium labeled Mebrofenin scan). The GBEF was assessed after fasting followed by a uniform fatty meal to identify patients with impaired GBEF. 38% was taken as a normal GBEF. The GBEF was reassessed after 6 months of GFD, in the subgroup with impaired GBEF at baseline. The Oro- Cecal Transit time (OCTT) was also estimated in all patients using Lactulose Hydrogen Breath Test.

Results: The mean age of study group was 9.06 ± 2.17 years with 46.2% belonging to the age group of 5-8 years and M:F ratio was 1.7: 1. 42% had classical celiac disease. Diarrhea (52%) was the commonest symptom followed by abdominal pain (40%). 82% (41 of 50) presented with poor growth and 36% (15 of 41) had no abdominal symptoms. Out of 50 subjects screened 8(16%) had decreased GBEF(< 38%) at baseline. Duration of illness was significantly longer (P value < 0.001), in children with decreased GBEF.

The percentage decrease in gall bladder volume (post fatty meal) was significantly lower in subjects with low GBEF as compared to group of patients with normal GBEF. The mean percent change(SD) in GB volume (post fatty meal) at baseline was 25.43% (21.60) whereas mean percentage change(SD) in GB volume (fasting to PP) after 6 month of GFD was 51.56% (10.58) and statistically significant. The mean GBEF was statistically lower in patients with impaired ejection fraction (n=8; 19.25) as compared to those with normal ejection fraction (n=42; 71.28) and the group as a whole (n=50; 62.96). The improvement in GBEF in the patients with impaired ejection fraction after gluten withdrawal was statistically significant.(p< 0.001;19.25 vs 76.25) and once again could be correlated with ultrasonography findings.

CD children with decreased GBEF also had significantly longer OCTT by Lactulose H$_2$BT (96 Vs 56 min; P,0.01), though there was no evidence of bacterial overgrowth.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal GB Function(42)</th>
<th>Impaired GB Function (8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBEF (%age) Mean (SD)</td>
<td>71.28 (13.48)</td>
<td>19.25 (12.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sonographic %age change of GB Vol. (fasting to PP): Mean(SD)</td>
<td>41.30 (19.5)</td>
<td>25.42 (21.60)</td>
<td>0.048</td>
</tr>
<tr>
<td>OCTT in minutes Mean (SD)</td>
<td>96 (13.82)</td>
<td>56.10 (11.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: The GB function is significantly impaired in 16% of children with CD and recovers completely on GFD. There was a very good correlation between GBEF assessed by Mebrofenin.
hepatobiliary scan and GB volume change by ultrasound. Hence ultrasound is an alternative tool for objective assessment of GB contractility. Children with impaired GBEF also had prolonged OCTT, in the absence of bacterial overgrowth assessed by H2BT.

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The role of environmental factors on the childhood celiac disease

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Objectives: This study was done to evaluate the impact of environmental factors on the occurrence of celiac disease in children.

Methods: All the patients diagnosed with childhood celiac disease (based on the revised ESGPHAN criteria) reporting in the department of paediatrics, from 1st January 2014 to 31st June 2015 and corresponding controls subjects (normal serum iTG and negative family history of celiac disease) were included in the study. The parents of patients and controls were interviewed as per the Performa. The data obtained was analysed with chi square test and t test.

Results: Sixty consenting patients with Childhood celiac disease and sixty controls were randomly divided into two equal groups based on age of presentation at diagnosis or age of symptoms (which ever being earlier) as ≤ 5 years (A) and > 5 years (B) were evaluated. The mean age of presentation was 2.7± 0.9 years in group A and 7.7± 2.1 in group B,respectively. No statistically significant difference was noted in socio-demographic characteristics. The most common presenting symptoms were abdominal distension (75%),chronic diarrhea(45 %) and failure to thrive(40%). Associated autoimmune diseases were common (20%).Family history of celiac disease was observed in 11.7 % of patients.No association was seen with celiac disease and the mode of delivery. All mothers breast fed their children(except 2 of group B). The duration of breast feeding was similar in the cases and controls.The age of introduction was earlier in patients with celiac disease as compared to the control group.The rate of infections and antibiotic use was however higher in the controls.

Conclusion: Earlier gluten exposure despite simultaneous breast feeding was associated with celiac disease. No association was observed between celiac disease and mode of delivery. Overall, early life infections were more common in controls than celiac disease patients.

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**GASTROENTEROLOGY - Coeliac disease**

**G-P-021**

**Intraepithelial junctions in coeliac disease - ultrastructural changes and serological markers of an impaired epithelial barrier**

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**Objectives and Study:** Epithelial cells and their intracellular junctions seem to play an important role in activation of processes leading to the pathology associated with coeliac disease (CD). It has been hypothesized that an early disruption of epithelial barrier, especially tight junctions (TJ) resulting in an increased intestinal permeability and transfer of gluten peptide into lamina propria could induce immune response to gluten and development of CD. The aim of this study was to analyze ultrastructural changes of intraepithelial junctions and serological markers of an impaired epithelial barriers: zonulin and intestinal fatty acid binding protein (I-FABP) in CD patients.

**Method:** Study included paediatric patients with recognized CD before introduction of gluten free diet (n=35), control patients age matched with functional gut disorders (n=49). I-FABP (Hycult Biotech) and zonulin (Immunodiagnostik AG) were measured by immunoenzymatic assays using commercial kits in sera of all children. Electron microscopy analyses were done in 15 children with active CD presenting histological changes at least as Marsh 3A and 9 children from control group. At least 10 intraepithelial junctions including TJ and adherence junctions (AJ) were analyzed in one patient. The width and the length of TJ and AJ were measured. CellSence (Olympus) program was used for morphometric analyses. Statistics was done using t test (Statistica 5.0). The study was approved by a local Ethics Committee.

**Results:** Ultrastructural analyses showed irregular and significantly shorter microvilli in brush border in CD patients compared to control group. TJ were significantly tighter (mean value (MV) was 9.03±1.03 nm; p=1.62634E-07) and shorter (MV=242.9±57.01 nm; p=0.019) in CD group than in controls (MV=10.22±1.7 nm and 266.6±49.5 nm, respectively), whereas adherence junctions were wider (MV=27.7±8.6 in CD versus 23.4±6.1 in controls) and shorter (MV=273.6±54.0 in CD versus 295.7±64.7 in controls). Dilatation of intraepithelial space was shown only in CD patients. Serological tests revealed no differences in zonulin levels between both groups (MV was 13.3±4.3 ng/ml in CD patients and 15.3±5 ng/ml in control group). In contrast I-FABP level was significantly (p=0.001) higher in CD patients (MV= 1538.0±924.0 pg/ml) compared with controls (MV= 359.0±228.9 pg/ml).

**Conclusion:** Despite significant changes in ultrastructure of intraepithelial junctions in CD it seems that TJ do not play so significant role in an increased epithelial permeability in patients with active CD.

The study was financed by the Children's Memorial Health Institute Grants No 236/15 and S156/2017.

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The prevalence of coeliac disease in children and adolescents with type 1 diabetes - a 10 years prospective study

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Objectives and Study: Type 1 diabetes (T1D) is one of the most common chronic conditions diagnosed in childhood and adolescence determined by insulin deficiency due to autoimmune destruction of beta-pancreatic cells. Coeliac disease (CD) and T1D are both multifactorial diseases, resulting from the combination of several genetic and environmental factors. The aim of this study is to show the prevalence of CD among children and adolescents with T1D in the last 10 years in Constanta County.

Method: We performed a monocentric study, which included 171 patients between 1 and 17 years with T1D, during January 2007- November 2017. According to ESPGHAN and ISPAD guidelines, we screened all patients for CD at the onset of diabetes and then during their follow up annually for the first 5 years and once every 2 years then, or whenever CD symptoms appear. We evaluated the presence of antibodies: autoantibodies against TG2 IgA (anti-TG2), endomysium IgA antibodies (EMA) and total immunoglobulin A (IgA) level.

Results: CD was found in 15 patients with T1D, with a prevalence of 8.7%. Higher incidence was found in girls (60%). Five of them were diagnosed at the onset at diabetes with a median age 5.1 years at onset of diabetes (min. 2.2 years; max.13.2 years). 6 patients were diagnosed one year after the onset of diabetes, 3 patients were diagnosed two years after onset and 2 patients were diagnosed after 3, respectively 4 years from onset. None of the patients had selective IgA deficiency. In 6 patients we found iron-deficiency anaemia, 6 patients with failure to thrive, 3 patients with behavioral issues such as anxiety, depression and aggressive behaviors. Recurrent episodes of hypoglycemic was found in all patients. The small bowel biopsy was performed in 10 patients (with an average value of anti-TG2- 103.4 U/ml). Histological findings were classified according to Marsh Type: 4 patients with Marsh3c, 3 patients with Marsh3b, 2 patients with Marsh3a and 1 patients with Marsh2. In 5 patients, biopsy was not performed, because of various reasons including parental choice, high levels of antibodies (>10 times of the normal range used by our biochemistry laboratory). 35% of the patients had vitamin D deficiency and 65% had vitamin D insufficiency. Because of the high risk of connections with other autoimmune disease, we tested also for autoimmune thyroiditis. 3 patients have found with the three autoimmune disorders, all of them with euthyroidism.

Conclusion: CD is an autoimmune disorder that occurs in people with genetic predisposition, which may present connections with other autoimmune diseases like T1D. Recognizing the importance of serological screening of CD in patients with T1D, helps to diagnose and treat CD, even if gastrointestinal symptoms may be missing.
Gastroenterology - Coeliac disease

G-P-023

MicroRNA expression profiling in children with coeliac disease

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Objectives and Study: Coeliac disease (CD) is a chronic enteropathy triggered by gluten proteins, characterized by altered immune responses in genetically susceptible individuals that results in damage to the bowel mucosa. MicroRNAs (miRNAs) play role in biological processes associated with the regulation of chronic inflammation and autoimmunity. Although lately there have been studies examining potential role of miRNAs in pathogenesis of autoimmune and inflammatory diseases and especially CD, their numbers are still limited. In this project, expression profiles of miRNAs were evaluated in children diagnosed with CD according to Marsh classification, and the possibility of utilizing them as novel marker were assessed.

Method: Study population included 33 children diagnosed with CD and another group of 33 children that went through upper gastrointestinal system endoscopy for other reasons and have normal biopsy results in Paediatric Gastroenterology Department of Celal Bayar University School of Medicine. miRNAs were isolated from the paraffin embedded tissue samples from each group followed by cDNAsynthesis. Six cDNA samples from each group were used on Human miFindermiRNA PCR Array. Analysis of the array data were performed online using the software provided by the manufacturer at http://www.sabiosciences.com/pcrarraydataanalysis.php. The highest expressed10 miRNA genes(hsa-miR-29b-3p, hsa-miR-30e-5p, hsa-let-7a-5p, hsa-miR-103a-3p, hsa-miR-27a-3p, hsa-miR141-3p, hsa-miR143-3p, hsa-miR-146a-5p, hsa-miR-194-5p, and hsa-miR-26a-5p) in patient groups that were statistically significant were validated by Real Time-PCR.

Results: When anemic CD patients were compared against the control group the hsa-miR-194-5p gene (fold-regulation value &lt; -2) was observed to be significantly under-expressed (p=0.008177). The genes of hsa-miR-29b-3p, hsa-miR-30e-5p, and hsa-miR-146a-5p were statistically significantly overexpressed in CD patients with constipation compared with the control group (p=0.036353, 0.046975, and 0.019412, respectively). Significant overexpression of hsa-miR146a-5p gene was detected in the control group compared with the Marsh2 and Marsh3a groups (p=0.004418 and 0.000306) while no significant gene expression was detected in the control group compared with the Marsh1 group. In comparison of the control group with the Marsh3b group hsa-miR-29b-3p, hsa-miR-30e-5p, hsa-let-7a-5p, hsa-miR27a-3p, hsa-miR141-3p, hsa-miR143-3p, and hsa-miR-146a-5p miRNA genes were significantly overexpressed (P &lt; 0.005). In the control group and Marsh3c comparison, the hsa-miR-194-5p gene was significantly under-expressed (P =0.015212).

Conclusion: Our results suggest that miRNAs can be used as a biomarker during the development and progression of CD.
GASTROENTEROLOGY - Coeliac disease

G-P-024

Quality of life for healthy siblings of children with coeliac disease in Turkey

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Objectives and Study: In the past century, the most common diseases in children and young adults have been shown to change from infectious diseases to chronic diseases. It is thought that children with chronic illness may cause changes in the quality of life of family members. Studies on the evaluation of children with chronic illness with quality of life are limited, different results are obtained and there is no study done about the quality of life of the siblings of children with chronic diseases in Turkey. Since geographic regions might affect health-related quality of life studies, health system and socioeconomic level differences, we planned to assess health-related quality of life in siblings of children with chronic physical disease in Turkey and herein we present data from healthy siblings of children with coeliac disease.

Method: We include children with coeliac disease, children with other chronic diseases and healthy children, who have at least one healthy sibling at home. The Pediatric Quality of Life Inventory (PedsQL) test has been performed to parents and/or healthy siblings (according to their age), including physical health score, psychosocial health score (calculated by taking the average of the emotional, social and school functional scores) and total score. The primary outcome point of the study was the assessment of health-related quality of life score of healthy siblings of children with coeliac disease and the comparison of healthy siblings of healthy children and the secondary endpoint was the comparison of healthy siblings of children with celiac disease with healthy siblings of other chronic childhood diseases. Statistical analyzes were performed using the SPSS for Windows 16.0 package program.

Results: Healthy siblings of 33 children with coeliac disease, and healthy siblings of 158 children with other chronic conditions and 100 healthy siblings of healthy children, have been evaluated. There was no statistically significant difference for age, gender, socioeconomic levels of the families, and education of parents between the groups (p> 0.05). According to individual response of healthy siblings, psychosocial health score and total score in celiac disease are higher than cerebral palsy, hematologic oncologic diseases, asthma, diabetes and epilepsy group and no difference was found between healthy children and celiac group. When the parental responses of healthy siblings were evaluated, total score was found to be low in all chronic disease groups (p<LT; 0.05) except coeliac disease group comparing the control healthy group (p>0.05).

Conclusion: It is seen that the siblings of children with celiac disease, the quality of health, including physically and psychosocially, is not affected. Quality of life of healthy siblings of children with celiac disease is better than other chronic conditions. While coeliac disease might results with permanent chronic dietary changes/restriction, these changes have no effect on healthy sibling’s quality of life scores.
GASTROENTEROLOGY - Coeliac disease

G-P-025

A comparison of growth parameters and anti-tissue transglutaminase levels in newly diagnosed coeliac children using the biopsy and non-biopsy methods over an 18-month follow up period

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Objectives and Study: Coeliac disease (CD) is an immune mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. The only known and effective treatment for CD is a strict, life-long gluten free diet (GFD). CD has many possible manifestations including, but not limited to, abdominal pain, diarrhoea, failure to thrive and short stature. Up to 2012, the only acceptable method for diagnosing CD was histological findings of changes corresponding with this illness in tissue biopsies obtained from the thin intestine. In 2012, the term non-biopsy diagnosis was introduced by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). When fulfilling certain strict criteria, the diagnosis of CD can be established without histological verification of the disease. The aims of this study are the comparison of growth parameters and rate of decline of anti-tissue transglutaminase antibodies (tTGA) levels between biopsy and non-biopsy diagnosed children during the first 18 months since the commencement of a strict GFD.

Method: Newly diagnosed children with CD were followed up at regular three-month intervals till the eighteenth month from establishing the diagnosis. Their growth parameters (height, weight and weight to height percentiles) and tTGA levels were evaluated at each visit. An F-test for testing equality in variances was used to test the hypothesis of equality of each parameter between the two cohorts. All children were diagnosed in adherence with the ESPGHAN guidelines.

Results: 195 newly diagnosed children with CD (average age 6 years and 10 months) between 01/2013 and 02/2016 were enrolled into the study. 88 of them were diagnosed with histological confirmation of this illness and 107 were diagnosed without a biopsy. These children were followed up at regular 3-month intervals. A statistically significant difference in growth, height and weight to height percentiles and tTGA levels at 18 months since the commencement of GFD, with a p-value < 0.05 in favour of the biopsy diagnosed children was found in all followed attributes.

Conclusion: An expected statistically significant difference in growth parameters was present between biopsy and non-biopsy groups at the time of diagnosis. This is given by the fact that children with non-biopsy diagnosed CD, mainly toddlers, are more ill than their biopsy diagnosed counterparts. A statistically significant difference in all followed parameters including tTGA levels in favour of the biopsy diagnosed group was still demonstrated at 18 months of follow up. These results go to show that non-biopsy diagnosed children require more time to catch up with their biopsy diagnosed counterparts surpassing the 18 months’ milestone. With a known tTGA half time ranging between 30 and 60 days, a question regarding the adherence level to a GFD in non-biopsy diagnosed children is in place.

This study was supported by grant RVO VFN 64165/2012.

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High risk of Coeliac Disease in HLA-DQ2 trans haplotype in a long-term study in a Spanish at- genetic-risk birth cohort

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Objectives and Study: Screening programs in at-risk populations have shown that HLA haplotype is an important population screening tool and can also individualize the patients follow-up according to their genetic risks. The aim of the current study was to perform a long-term coeliac disease (CD) screening in a cohort of HLA-DQ2 + children and to assess the influence of each risk genotypes on its development.

Method: In 2004, a CD genetic-risk HLA-DQ2 cohort was selected. The first CD screening was performed at the age of 2-3 years and 8-10 years later a second screening was repeated. Anti-TG2 antibody detection (immunoglobulin IgA/IgG/IgM) was performed in a whole blood sample taken from a finger prick at the point of contact using a rapid test kit (POC test). These results were confirmed by serum IgA anti-TG2 and IgA EMA determination. CD final diagnosis was carried out by intestinal biopsy. For High-resolution HLA typing samples of saliva were collected by oral mucosa brushing. The HLA genotype was carried out by PCR followed by hybridacion with allele-specific probes. According to the different genotypes 4 groups were defined: G1: DQ2.5/DQ2.5or DQ2.5/DQ2.2, G2: DQ2.2/DQ7 (DQ2.5 trans), G3: DQ2.5/X y G4: DQ2.2/X. Statistical analysis was performed using the SPSS 22.0 version (SPSS Inc.Chicago IL, USA).

Results: The first screening (2-3 years of age) was performed to 262 HLA-DQ2+ children (15 of them with final CD diagnosis). 185 children (75% of the genetic risk birth cohort) were included in the second screening. At the age of 10-12 years, 6 new CD cases have been diagnosed. The overall prevalence after at least 10 years of follow-up in the at-risk cohort was 8% (95%CI 5.3-11.9) or 1/12.5. The general population prevalence is 1.55% (95%CI 1,01 - 2,38) or 1/64. The ratio between the symptomatic group and the screening group was 1/1.5 at 2-3 years and 1/1.1 at 10-12 years. CD cumulative incidence at 3 years was 5.72% (IC 95% 2.6-12.1) and at 10-12 years was 10% (IC 95% 2.6-13.7).

The distribution of genotypes in the whole HLA-DQ2 cohort was: 22% carried G1 homozygous genotype (DQ2.5/DQ2.5 or DQ2.5/DQ2.2), 10.5% DQ2.5 trans, 63% DQ2.5 cis and 4.5% DQ2.2/X. 33.3% of the CD children carried homozygous G1 genotype compared to 21.1% of the healthy children. Although this difference was not statistically significant, if we consider just the DQ2.5/DQ2.5 genotype, the risk for CD to be developed is 4.09 (95% CI 0.9-17.2) P= 0.039. 24% of the CD children carried HLA DQ2.5 trans genotype compared to 8.9% of the healthy children, OR 3.18 (95% CI 1.1-9.8) P= 0.035. In our cohort, children carrying the homozygous genotype and DQ2.5 trans were earlier and more frequently diagnosed of CD during the follow-up.
**Conclusion:** In this at-genetic-risk birth cohort in general population the most important genotypes in the development of CD were homozygous HLA-DQ2.5 and also as in other mediterranean areas DQ2.5 trans. A repeated screening should be consider in the follow-up of these at-risk children.

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Clinical profile of Coeliac Disease in a long-term study in an at-genetic-risk birth cohort

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Objectives and Study: Screening studies provide useful information about the complete clinical spectrum of coeliac disease (CD) and allow clinicians to know the symptoms and signs of the disease that are often unnoticed. The aim of this study was to clinically characterize patients diagnosed with CD in a long-term study in an at-genetic-risk birth cohort.

Method: CD screening was performed in a HLA-DQ2 (+) risk cohort at 2-3 years and at 10-12 years of age. 2 groups of children were examined: the screening and the symptomatic group. In the screening group, a point-of-contact test (POC test) was implemented to detect anti-TG2 (IgA/IgM/IgG). In children with a positive POC test, serum anti-transglutaminase 2 (anti-TG2) and endomysial antibodies (EMA) were performed to confirm results. Positive cases were referred to the Paediatric Gastroenterology Unit and were retested 3 months later. The symptomatic group, consisted of children referred to our Unit by their primary-care paediatricians after detecting CD serology positivity. Final diagnosis was confirmed in all cases by intestinal biopsy. During the visits, a registration form was filled out containing age, sex, CD-associated conditions and symptoms and signs related to CD. Anthropometric measures were obtained, using age- and gender-matched Z scores.

Results: The overall CD prevalence after at least 10 years of follow-up is 21/262 HLA-DQ2 (+) children: 8% (IC95% 5.3-11.9) or 1/12.5: 10 children were diagnosed after presenting symptoms and 11 by screening. The ratio between the symptomatic group and the screening group was 1/1.5 at 2-3 years and 1/1 at 10-12 years. In the screening group only 45.5% were asymptomatic ± ferropenia, however abdominal distension was present in 36.5%. In the symptomatic group, half of the children had classic symptoms of CD (all of them diagnosed in the first screening) and those diagnosed later presented in all cases abdominal pain and half of them also constipation. Of the total CD children, 30% had classic symptoms (chronic diarrhea, weight loss and abdominal distension), 30% non-classic symptoms (abdominal pain ± constipation, weight loss or short stature), 20% were asymptomatic and another 20% had abdominal distension as the only symptom. Anthropometric measures were normal in all patients except in one girl diagnosed in the second screening with Z score of height -2.06. A significant improvement in weight was observed in the screening and symptomatic groups one year after the diet treatment while a significant height increase was observed in the screening group.
[Clinical profile in the screening and the symptomatic group]

**Conclusion:** In the current study the children were mainly symptomatic. This could be related with an active search of symptoms in screening studies. In order to ascertain the clinical response on a gluten free diet a follow up is necessary.

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Objectives and Study: Coeliac disease is a systemic immune-mediated disease with a multifactorial etiology including a strong genetic component since the disease rarely develops without the presence of specific HLA alleles. Specific HLA haplotypes have the ability to efficiently present gliadin peptides to reactive T cells in the gut. Approximately 90% of celiac patients express HLA-DQ2 heterodimer in cis (DRB1*03:01-DQA1*05:01-DQB1*02:01, DR3-DQ2 haplotype) or in trans (DRB1*07-DQA1*02:01-DQB1*02:02, DR7-DQ2; DRB1*11/12-DQA1*05:05-DQB1*03:01, DR5-DQ7). The remaining of the patients present HLA-DQ8 heterodimer (DRB1*04-DQA1*03:01-DQB1*03:02, DR4-DQ8 haplotype). The aim of this study was to analyze the HLA DQ distribution and determine the disease risk conferring by the different HLA DQ types. For this purpose, 99 unrelated celiac patients diagnosed in a single center in Northern Greece and fulfilled the ESPGHAN diagnostic criteria, (66 female and 33 male) were subjected to analysis. One hundred and twenty healthy unrelated individuals served as controls.

Method: DNA was isolated from peripheral blood. HLA-DQB1, DQA1, DRB1 genes were typed by PCR-SSP using commercially available kits. Differences were analyzed by chi-squared or Fisher’s exact test. Disease risk was expressed as 1:100, where N is the number of subjects among which is present one patient. Considering a disease prevalence of 1:100 in the general population, N was calculated as a percentage of controls with that particular haplotype multiplied by 100 and divided by percentage of patients with the same HLA-DQ type.

Results: The HLA-DQ2 (cis or trans) and/or the DQ8 were detected in 98 patients (99%) and in 44 (37%) controls. Two alleles coding for at-risk DQ beta chains (*02/*02, *02/03:02, or *03:02/03:02) were found in 44.4% of the cases and 3.3% controls leading to a very small p value (p=3.51x10^-14). The DQB1 *02/*02 combination was found in 21 of 99 patients and 4 of 120 controls (p=3.2x10^-5) and DQB1*02/*03:02 was observed in 20 of 99 cases and 1 of 120 controls (p=5.2x10^-7). The only patient who did not carried neither DQ2 or DQ8 was homozygous for DR11-DQ7 carrying half of the DQ2 molecule in homozygosis. Based on the HLA-DQ typing, we obtained a gradient of disease risk ranging between 1:7 and 1:5445. The highest risk value was for subjects heterozygotes for HLA-DR3-DQ2/DR4-DQ8 (1:7) followed by: DR4-DQ8/B1*02 pos (1:10), DR3-DQ2/ B1*02/*02 (1:16), DQ2 trans (DR7-DQ2/DR11-DQ7) 1:30. The presence of DQ8 only without B1*02 led to the disease likelihood of 1:108 while the presence of beta chain *02 (usually presented in haplotype DR7-DQ2) only without any of other susceptible alleles resulted in 1:208 disease risk.

Conclusion: In our study the presence of both DQ2 and DQ8 haplotypes resulted in the highest genetic predisposition (1:7) while the next most predisposing genotype was DQ8/B1*02 (1:10) presenting an effect of DQ8/B1*02 also evident in absence of DQA1*05 as the occurrence of DQB1*02 allele (usually on DR7-DQ2 haplotype) in DQ8 subjects raised the risk from 1:108 to 1:10. We suggest that asymptomatic relatives of patients carrying DQ2/DQ8 and DQ8/B1*02 should be monitored more often because of the highest disease risk with these haplotypes for early diagnosis.
Iodine deficiency status in coeliac children at diagnosis: case-control study. Preliminary data

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Objectives and Study: It's well known the association between coeliac disease (CD) and autoimmune thyroid disease but in several cases non-autoimmune subclinical hypothyroidism have been described in coeliac children. It is assumed that non-autoimmune hypothyroidism could be caused by a reduced biosynthesis of thyroid hormones, due to intestinal malabsorption of iodine. Aim of this study is to check the iodine deficiency status in coeliac children at diagnosis, while on a free diet.

Methods: At present the study includes 11 coeliac patients defined as “cases” (4 boys and 7 girls, aged 3-18 years; mean age 7.5 years), and 11 healthy first-degree relative (controls). The diagnosis of CD was made according to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria. We excluded patients presenting other autoimmune disease or following thyroid hormone treatment before the diagnosis of coeliac disease. Initial data collection included patients' clinical history, growth assessment, complete thyroid function, autoimmunity tests. We tested urinary iodine concentration from 24-hour sample both in cases and controls in order to compare urine iodine excretion in healthy and coeliac people and to exclude inadequate iodine dietary intake. Urinary iodine concentration was obtained with colorimetric determination and spectrophotometric detection.

Results: Most of the patients were asymptomatic; they have been diagnosed after routinely blood test. Three of them had chronic abdominal pain and one of them had also failure to thrive. All patients had normal thyroid function and negative anti-thyroid antibodies titre. Seven patients and five controls were iodine insufficient (p=0.39). Six patients had moderate deficiency of iodine level (range: 20 to 49 µL/24h) while only one patient had slight deficiency (range: 50 to 99 µL/24h). All the four iodine insufficient controls had a slight deficiency. The urinary iodine concentration was 79.18 µL/24h (SD=51.04) in the coeliac group and 114.00 µL/24h (SD=54.11) in the control group (p=0.13). Thyrotropin was 3.18 µUI/ml (SD = 1.25) in the 4 patients with iodine sufficiency and 2.05 µUI/ml (SD = 0.69) in the 7 patients with iodine insufficiency (p =0.08).

Conclusion: These preliminary data show that iodine deficiency status is similar between patients and controls, suggesting that there is no impairment of iodine absorption accounting for thyroid impairment. However, there are preliminary results and we need to keep on recruiting patients to reach a larger sample power to verify again the initial assumption.

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A standardized short dietary questionnaire for adherence to gluten-free diet in children with coeliac disease

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Objectives and Study: Strict adherence to gluten-free diet (GFD) is the cornerstone for the treatment of coeliac disease (CD). A standardized short Structured Dietary Questionnaire (SDQ) for children has recently been published. This study aimed to 1) Compare the SDQ with an Unstructured short Dietary Interview as it is performed in clinical practice (UDI); 2) Relate the outcome of both interviews with the level of coeliac antibodies and/or micronutrient deficiencies.

Method: Children with a confirmed diagnosis of CD and their caregivers completed the SDQ and underwent a UDI by a medical doctor (MD) who was blinded to the results of the SDQ. At the same time, serum levels of zinc, ferritin and haemoglobin levels in combination with anti-tissue Transglutaminase antibodies (tTG) were determined. Low iron status was defined as ferritin &LT; 7 µg/L, low zinc was defined as serum zinc &LT; 70 µg/dL. Positive celiac antibodies was defined as tTG ≥10 U/mL. Weight for age (WFA), height for age (HFA) and BMI z scores were calculated according to national reference charts.

Results: In total, 35 children (25 girls) were included with a mean (SD) age of 8.5 (3.6) years. The median (Q1;Q3) time since diagnosis was 3.0 (1.4;4.7). Mean (SD) WFA, HFA and BMI z scores were significantly (p-value for all < 0.01) lower at the time of diagnosis than at present time: WFA -1.1 (1.0) vs -0.5 (0.9); HFA -0.9 (1.2) vs -0.5 (1.1) and BMI -0.9 (1.1) vs -0.3 (0.9). Strict adherence to GFD was determined according to the SDQ in 13 (37%) children, adherence to GFD with errors in 20 (57%) and non-adherence in 2 (6%). UDI concluded strict adherence for 24 (69%), adherence with errors in 10 (29%) and non-adherence in 1 (3%). Perfect agreement between both interview methods was present for 20/35 (57%), corresponding with a \( \kappa \) (95% CI) of 0.26 (-0.0;0.6). Of the children who were diagnosed with CD ≥1 year ago, only 1/28 had positive tTG; this child was non-adherent to GFD according to both SDQ and UDI. C-reactive protein levels were below 5 mg/L for all children. Zinc deficiency was present in two children; one was classified as non-adherent and one as adherent with errors by both interview techniques. Iron deficiency (low ferritin in combination with anemia) was present in only one child, who was strictly adherent according to SDQ and adherent to GFD with errors according to UDI.

Conclusion: The standardized short dietary questionnaire identifies more children with coeliac disease as adherent to GFD with errors than an unstructured short dietary interview. Reported errors in dietary adherence are not always accompanied by a positive tTG. The presence of micronutrient deficiencies was low in our cohort of children with CD. Due to the low number of children with positive antibodies and/or micronutrient deficiencies, this study was unable to determine which of both interviews should be preferred.

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Objectives and Study: The study aim is to compare the cost, availability and nutritional composition of traditionally wheat based manufactured gluten-free (GF) products with their gluten-containing (GC) counterparts, provided by food retailers (physical stores and online).

Method: A cross-sectional survey of 26 food categories was conducted in May 2017, data was collected on the cost, availability and nutritional composition of in excess of 1,000 GF and GC foods. Food categories included traditionally wheat based and everyday foods usually containing gluten. Fifty physical stores were surveyed, inclusive of convenience stores, budget supermarkets, regular supermarkets, quality supermarkets and health food shops (10 in each category). In addition, online retailers of manufactured GF products which offered a delivery service to the areas under study were also included.

Results: A third of all stores surveyed did not stock any traditionally wheat based manufactured GF items, this was comprised of budget supermarkets and convenience stores. The online GF food suppliers superseded all of the physical stores in the number of manufactured GF items available. However, over half of the GF items were more expensive in online stores than in regular supermarkets. In fact, 74% of GF foods surveyed were more expensive than their GC counterparts, including food staples such as GF bread and bread rolls were 294-449% more expensive than the GC counterparts (p&LT; 0.001), plain flour 94% (p=0.006) and flaked cereals 93% more expensive (p< 0.001). Nutritional composition comparison revealed higher energy, fat and saturated fat and less protein content for surveyed manufactured GF products.

Conclusion: Availability of manufactured GF products remains poor, especially in convenience stores and budget supermarkets, serving those from poor socio-economic cohorts, the elderly and physically disabled. The stores where availability has improved from previous published findings are associated with the greatest additional cost. The inferior comparative nutritional quality of manufactured GF products emphasises need for those on a medically indicated GFD to be advised and monitored by adequately trained health professionals and also provides evidence towards dispelling false claims that removing gluten from the diet has health benefits.

Disclosure of interest: £1000 grant from Coeliac UK for travel costs and conference fees

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Female predominance in children with undetected coeliac disease: a systematic review and meta-analysis

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Objectives and Study: Research on gender differences in screen detected coeliac disease is lacking. Studies on diagnosed populations suggest a female predominance, but some individual screening studies allude to boys being just as affected as girls. We sought to explore gender differences in coeliac epidemiology in children on a large scale by conducting a systematic review of the literature and a meta-analysis of pooled outcomes.

Method: The search encompassed MEDLINE, Embase, Scopus, and Cochrane databases from inception to May 2017, for studies of undiagnosed or screen detected coeliac disease epidemiology. Studies met inclusion criteria if they included only children, performed a screening and confirmatory test (with small intestine biopsy or second serological study), and provided complete gender data. Exclusion criteria were samples of referral, high-risk, or specific populations, as our goal was to quantify rates in a general paediatric population. Titles, abstracts, and articles were considered by 2 independent reviewers and data extraction was completed on a standardized form. Quality of the study and risk of bias were assessed for each included article. The primary outcome was relative risk of undetected coeliac disease for girls compared to boys expressed as a ratio. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Review Manager 5.3 software was used for all analyses.

Results: The search identified 4,245 articles and 28 met inclusion criteria. The meta-analysis was performed on 84,073 paediatric subjects (age range 0-18; majority primary school aged; females 37,456, males 46,617). The rate of undetected coeliac disease in girls was 0.87% and in boys was 0.45% with the pooled prevalence (p< 0.00001). The relative risk for girls was 1.79 (95% CI 1.40-2.28) when comparing girls to boys [Figure]. The I² was 34% indicating low between study heterogeneity. Looking at the cumulative body of evidence, the majority of studies were rated as good quality (57%), with others rated as fair. The risk of bias was low in most studies (68%) with a few at moderate risk (32%) when using standardized rubrics. Publication bias was evaluated through visual inspection of a funnel plot, which was symmetric, arguing for low likelihood of bias in publication.

Conclusion: This study confirms that coeliac disease is more common in girls than boys - not only in diagnosed but in general screened populations as well. This finding could have clinical implications in terms of screening, diagnosis, and management. For example, physicians should maintain a higher index of suspicion for coeliac disease in girls. Possible explanations for this result include differences in exposure triggers, up-regulation of gene expression, and variations in immune function based on gender. Further research is needed to identify why this disparity exists.

Figure: Forest Plot
### Table

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**Total events**: 304

**Heterogeneity Test**: $I^2 = 37.51$, $Q = 37.31$, df = 23 ($P = 0.00$); $I^2 = 94%$

**Test for overall effect**: $Z = 4.49 (P < 0.00001)$

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Adherence to diet treatment in adolescents with celiac disease and relationship of family functioning and psychiatric symptoms

Miray Karakoyun¹, Gonca Ozyurt², Yeliz Cagan Appak³, Sermin Yalin Sapmaz⁴, Guzide Dogan⁴, Masallah Baran², Erhun Kasırga⁴

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Objectives and Study: Celiac disease; is a small bowel disease that occurs in congenital predisposing individuals at any age. It is seen at a frequency of 100 people. The only treatment for celiac disease is diet. It requires a lifetime gluten-free diet. Psychiatric diseases such as depression and anxiety can be seen in celiac patients, as stated in the literature. In this study, it was aimed to determine the effects of depression, anxiety, diabetic compliance and family functioning in adolescents diagnosed with celiac disease.

Method: A total of 35 adolescent patients were included in the study with age between 12 and 18 years who were followed up with the diagnosis of celiac disease. Diagnostic age, diagnostic symptoms, Marsh stages were recorded. Height and weight measurements were made in the outpatient clinic and celiac serology test was taken. 47 cases were taken as a control who applied to pediatric outpatient clinics in our hospital. Beck depression scale, strength and difficulties questionnaire, family assessment questionnaire were performed by the infant child psychiatrist.

Results: 31 patients were Marsh 3 and 4 patients were Marsh 2 Celiac disease in the study. 23 (65.7%) of the patients were female, 12 (34.3%) were male and the mean age was 15.3 ± 2.01 di. The mean age of the control group was 15.9 ± 1.36. 29 of the patients were students, 4 were working, and 2 were unemployed. 15 patients were completely following their diet. The mean duration of sleep was 8.4 ± 1.26.

Compared with the beck depression scale, those with celiac disease had statistically significant higher scores than the healthy controls. On the family assessment scale, communication, emotional and general subscales, the family of the children of the celiac group had statistically significant high scores. When the cases and control group were assessed by the strength and difficulties questionnaire, it was determined that adolescents with celiac disease had more difficulties in emotional and social situations. The strengths and difficulties questionnaire subscale scores and p values are shown in the table below.

When celiac diagnosed are examined as those who adhere to the diet and those who do not, there was no statistically significant difference between depressive characteristics, family functioning and strengths and difficulties questionnaire subscales.

Conclusion: The treatment of celiac disease is fed with a lifelong gluten-free diet. This can lead to anxiety and depression, especially in the adolescent age group.

Contact e-mail address: miraykarakoyun@hotmail.com
Rising prevalence of coeliac disease is not universal and repeated testing is needed when screening populations

Rachel Levinson Castiel1, Rami Eliakim4, Eilat Shinar2, Tsachi Tsadok Perets3, Olga Layfer3, Nina Levhar4, Michael Schvimer5, Lubac Marderfeld1, Shomron Ben-Horin4, Raanan Shamir1

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2Magen David Adom, Ramat Gan, Israel
3Rabin Medical Center, Petach Tikva, Israel
4Sheba Medical Center Tel Hashomer, Ramat Gan, Israel
5Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Objectives and Study: Recent studies suggest that the prevalence of coeliac disease (CD) is rising. We established the prevalence of CD in Israel in blood donors in 2002. Our aim was to examine whether the prevalence of CD and CD autoimmunity has changed over time by performing a repeated prospective study of blood donors.

Method: Serum samples from 1908 healthy volunteer blood donors were tested for anti Tissue transglutaminase antibodies (TTG). Positive samples were tested for antiendomysial antibodies (EMA). All donors with positive TTG >3 upper limit of normal (ULN), were referred for intestinal biopsy. Donors with positive TTG< 3ULN were asked to repeat serology.

Results: Overall, 32 donors had abnormal TTG (1.68%). Eight donors had TTG>3XULN (0.42%), two of them with TTG>10XULN, while 24 donors had TTG<LT; 3XULN (1.26%). Most of the donors with positive TTG<LT; 3XULN had negative TTG levels on repeated testing (18/19). CD was diagnosed in 4 donors with positive TTG, establishing a prevalence of 1.68% (95% CI 1.15-2.3) for CD autoimmunity and 0.21% for CD (95% CI 0.07-0.5%). All diagnosed CD donors had positive EMA, and all others but one donor who refused biopsy, did not.

Conclusion: The prevalence of CD in blood donors in Israel did not rise in the last 15 years, suggesting that the increased prevalence of diagnosed CD is mainly due to increased awareness. As most of the donors with TTG<LT; 3XULN were EMA negative and had negative TTG testing on repeated serology, repeated TTG testing is needed when screening population for CD.

Contact e-mail address: rachellileca@gmail.com
Clinical presentation and long-term prognosis of coeliac disease in patients diagnosed in early childhood

Laura Kivelä¹, Alina Popp¹, Sara Koskimaa¹, Katri Kaukinen², Kalle Kurppa¹

¹University of Tampere and Tampere University Hospital, Tampere, Finland
²University of Tampere, Tampere, Finland

Objectives and Study: Presentation and long-term prognosis of coeliac disease diagnosed in early childhood are scarcely studied. It is particularly unclear how these individuals, who do not remember their diagnosis and benefits of the treatment, adhere and experience challenging gluten-free diet as an adult. We investigated these issues in a large cohort of currently adult coeliac patients diagnosed in childhood.

Methods: Comprehensive medical data of 307 adult patients diagnosed in childhood between years 1956-2000 were collected from patient records. Furthermore, they were sent a questionnaire evaluating a variety of health and lifestyle characteristics and experiences of gluten-free diet. Current symptoms and quality of life were measured by validated Gastrointestinal Symptom Rating Scale (GSRS) and Psychological General Well-Being (PGWB) questionnaires. Next, all results were analyzed between patients diagnosed in early (≤3.0 years) and later (3.1-17.8 years) childhood.

Results: Sixty-nine (22%) patients were diagnosed before and 238 (78%) after three years of age. Subjects with early diagnosis had more advanced intestinal damage (total villous atrophy 46% vs 39%, p=0.048) and more often gastrointestinal presentation (69% vs 45%, p=0.002), growth disturbances (75% vs 42%, p=LT 0.001) and severe symptoms (25% vs 5%, p=LT 0.001) at diagnosis, whereas there were no differences between the groups in year of diagnosis, gender distribution or presence of anemia. Altogether 130 adults returned the follow-up questionnaires. Of them, the early diagnosed patients (n=35) were currently younger (34.2 y vs 37.5 y, p=0.012) and more often students (26% vs 7%, p=0.012) and had less co-existing chronic diseases (26% vs 50%, p=0.015) than those diagnosed later in childhood (n=95). The groups were comparable in work status, presence of children and coeliac disease in the family, regularity of exercise, body mass index, smoking, experienced health and health concerns, implementation of follow-up, and adherence and experiences of dietary treatment. There were also no differences in current GSRS and PGWB scores.

Conclusions: Younger age at diagnosis is associated to more severe presentation of coeliac disease. However, neither this nor the lack of memories about the diagnostic process are reflected in the long-term prognosis or treatment outcomes; in fact, early diagnosis may even protect from coexisting other chronic diseases.
GASTROENTEROLOGY - Coeliac disease

G-P-036

Long term follow-up of pediatric Celiac Disease patients after transition to adult care

Michal Kori1, Sivahn Goldstein1, Lilach Hofi1, Chani Topf-Olivestone1

1Kaplan Medical Center, Rehovot, Israel

Objectives and Study: Follow up of Celiac Disease (CD) patients is challenging. Proper surveillance should include assessment of adherence to a gluten-free diet (GFD), resolution of symptoms, adequate growth and pubertal development and prevention of complications. Yearly follow-up is recommended. Data on follow-up after transition from pediatric to adult care is scarce. Our primary aim was to evaluate whether pediatric CD patients maintain adherence to GFD and continue medical follow-up after transition to adult care.

Methods: A retrospective review of 495 pediatric CD patients diagnosed and followed at a single Pediatric Gastroenterology Center between December 1998 and October 2017. Out of this cohort, patients older than 18 years were identified. Data concerning presenting symptoms, adherence to GFD and complications before and after age 18 years was extracted from hospital records and from a national electronic data base "Ofek". This database enables to review laboratory tests performed throughout the country, clinic visits and additional diagnoses given over time.

Results: Data regarding 108 patients older than 18 years was available, 65 (60.2%) were female. (F/M ratio 1.5). The median age at diagnosis was 12 (9m-18y), the median current age 23 (18-38y) with a median of 11.3 (2-36) years of disease duration. Presenting symptoms included: Abdominal pain 47 (45.2%), abdominal distention 10 (9.6%), diarrhea 34 (32.7%), constipation 6 (5.8%), nausea and vomiting 20 (19.2%), FTT or poor weight gain 37 (35.6%), short stature 25 (24%), iron deficiency anemia 53 (51.0%), autoimmune thyroid disease 3 (2.8%), type 1 diabetes mellitus 5 (4.7%), genetic syndromes (Down or Turner syndrome) 4 (3.7%) and a first-degree relative with CD 10 (9.3%). Until 18 years of age, adherence to GFD was reported as good to excellent in 83/105 (79%), non-adherence in 22/105 (21.1%). Celiac serology normalized in 87/106 (82.1%), within 2 years in 66/87 (75.8%). In 84/99 (84.8%) complete resolution of symptoms was reported. In 52/84 (78.8%) symptoms resolved within a year. Most patients 79/108 (72.2%) had yearly follow-up visits. There was no correlation between age or symptoms at diagnosis and adherence with GFD. After the age of 18 years, adherence was measured by serology testing. 78/108 (72.2%) patients were tested, with negative serology in 61/78 (78.2%). Testing was performed every 1-3 years in 46/78 (59%). Most patients 77/108 (71.5%) were followed by their primary care physician and never visited a GI clinic as adults. Only one patient developed CD related complications (alopecia) after the age of 18, this patient was non-compliant. In the vast majority of patients 56/60 (93.3%) with negative serology as children, serology remained negative as adults. In contrast, in only 4/16 (25%) patients with positive serology as children the serology became negative as adults (P&LT; 0.001).

Conclusions: Adherence to GFD before the age of 18, positively predicts the continuation of adherence as adults. Even though most adults who followed a GFD did not attend GI clinics, most performed follow-up serology tests, which were negative. Our study emphasizes the need for meticulous follow up of CD patients during childhood in order to achieve long-term adherence with GFD as adults.

Contact e-mail address: korifamily@yahoo.com
Nation-wide survey on the utilisation of diagnostic tools for paediatric coeliac disease in 2016-2017

Ilma Rita Korponay-Szabo¹, Judit Gyimesi², Petra Riznik¹⁰, Zsófia Barkasi-Szabó¹, Márta Balogh³, István Tokodi⁴, Éva Pollák⁵, Ildikó Guthy⁶, Ágnes Horváth⁷, Katharina Werkstetter⁸, Sibylle Koletzko⁸, Jasmina Dolinsek⁹, Jernej Dolinsek¹⁰, Piroska Bódi¹¹, Ildikó Kis¹², Judit Bajor¹³, Noémi Csoszánszk¹⁴, Éva Nemes¹, Orsolya Kadenczki¹, Judit B. Kovács²

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²Heim Pál Children's Hospital, Budapest, Hungary
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⁴Fejér County Szent György Hospital, Székesfehérvár, Hungary
⁵Magyar Imre Hospital, Ajka, Hungary
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¹³University of Pécs, Pécs, Hungary
¹⁴Semmelweis University, Budapest, Hungary

Objectives and Study: ESPGHAN allowed in 2012 to confirm the diagnosis of coeliac disease (CeD) without biopsy in children with CeD-relevant symptoms (as defined in Husby, JPGN 2012) and serum anti-transglutaminase antibody levels exceeding 10 times the upper limit of normal (High TGA+) in whom endomysial antibodies (EMA) are positive and who carry HLA-DQ2 or DQ8. In this study we explored how these criteria are followed in clinical practice.

Method: Paediatric gastroenterologists in Hungary were asked to upload medical data of their patients diagnosed with CeD between January 2016-April 2017 concerning disease presentation, antibody, histology and DQ results into an anonymised web database developed during the Interreg Central Europe „Focus in CD” project and utilised before in Croatia, Germany, Italy and Slovenia. Here we present the results of the Hungarian subgroup.

Results: 27 gastroenterology services representing all counties in Hungary uploaded altogether 654 patients’ data diagnosed in the last year with CeD, of whom 566 were below 18 years of age (median 8 years, range 1-18). Biopsy was performed in 435 children (76.8%), which showed Marsh 2-3 lesions or villous atrophy by other grading in 413 (95%), Marsh 1 in 12 (2.7%), or the biopsy specimen was not evaluable in 10 (2.3%). In 26 children biopsy was not possible because of the parents’ refusal or other medical reasons. In other 105 patients (18.5%) the no-biopsy approach was applied, in whom EMA was tested in 92/105 (87%) and HLA-DQ was determined in 94 (89.5%). The most frequent reasons for the lack of genetic testing were high costs not supported by insurance, and for replacement of EMA the use of DGP in 2 centers. Altogether 75% of children had all the criteria required by the 2012 ESPGHAN guidance for the non-invasive diagnosis, while 84% fulfilled the protocol of having CeD-relevant symptoms, High TGA+ and EMA+ result indicating a safe CeD diagnosis even without HLA-testing by recent prospective studies (Werkstetter, Gastroenterology 2017). In these cases, HLA-DQ testing did not add to the diagnosis in our study either.
<table>
<thead>
<tr>
<th>Positive (% of all in the group)</th>
<th>Biopsy performed (n=435)</th>
<th>Biopsy refused or contraindicated (n=26)</th>
<th>No-biopsy approach (n=105)</th>
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<tr>
<td>CeD-relevant symptoms</td>
<td>336 (77.2%)</td>
<td>20 (76.9%)</td>
<td>99 (94.3%)</td>
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<td>- and High TGA+</td>
<td>235 (54.0%)</td>
<td>17 (65.4%)</td>
<td>98 (93.3%)</td>
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<td>- and High TGA+ plus EMA+</td>
<td>188 (43.4%)</td>
<td>17 (65.4%)</td>
<td>88 (83.8%)</td>
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<td>- and High TGA+ plus EMA+ and DQ2/DQ8</td>
<td>10 (2.3%)</td>
<td>11 (42.3%)</td>
<td>79 (75.3%)</td>
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</tbody>
</table>

[Components of the CeD diagnosis]

**Conclusion:** The majority of practising paediatric gastroenterologists in Hungary follow well the ESPGHAN criteria in making the no-biopsy diagnosis of CeD. As omitting HLA-DQ testing does not compromise accuracy, this would make the no-biopsy approach more broadly available also in countries with less financial resources. Of note is that also 43% of children who currently undergo biopsy already do qualify for these less strict criteria even before the endoscopy, but a final diagnosis also must depend on collaboration and acceptance by parents.

**Grant support:** Interreg Central Europe CE111 Focus in CD, NKFI120392 and EFOP-3.6.1-16-2016-00022 projects.

Acknowledgement to other colleagues contributing with less than 15 patients: Ágota Mónus (Eger), Ildikó Rosta (Hatvan), Margit Lőrincz (Heim Pál, Budapest), Gábor Veres and Rita Lippai (Semmelweis University, Budapest), Erzsébet Gelencsér (Kaposvár), Éva Kosaras and Erzsébet Szakos (Miskolc), András Tárnok (Pécs University), Noémi Vass (Szeged University), Katalin Szabados and Laura Sándor (Szolnok), László Gárdos (Zalaegerszeg)

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Quality of life in children with celiac disease in clinical manifestation period

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²Russian Medical Academy of Postgraduate Continuing Education, Moscow, Russian Federation

Objectives and Study: A comprehensive analysis of quality of life (QoL) in children and adolescents with active celiac disease. Celiac disease in children is an urgent medical and social problem; this disease is associated with physical, emotional and social limitations. The use of such a complex criterion as QoL, allowing the assessment of the patient's mental and social state, is of priority in modern medicine.

Method: 57 children and adolescents aged 2 to 18 years old with active celiac disease were involved in the study. The diagnosis was made in accordance with the ESPGHAN clinical laboratory and morphological criteria (1990, 2012). Patients included 22 (39.0%) boys and 35 (61.0%) girls. Three age groups were outlined: 2–4 year-old - 32 (56.0%); 5–7 year-old - 11 (19.0%); 8–18 year-old - 14 (25.0%) subjects. 187 children and adolescents aged 2 to 18 years old were included in the control group. The assessment of QoL was performed using the PedsQL 4.0 questionnaire, including physical functioning (PF), emotional functioning (EF), social functioning (SF), and role functioning (RF). Both parent and children forms of the questionnaire were used.

Results: The interpretation of questioning results for parents of children aged 2 to 4 years old showed that the following parameters decreased: PF - 72.4% (p<0.001), EF - 48.6% (p<0.001), RF - 46.6% (p<0.001), SF - 80.9%, which was noted while comparing patients to healthy children; the overall assessment of QoL parameters was at 66.0% (p<0.001). According to the children's opinion, the QoL parameters in the age group 5–7 years old were significantly decreased due to PF - 57.4% (p<0.001), EF - 52.7% (p<0.002), SF - 63.6% (p<0.05), RF - 60.9%; the overall assessment corresponded to 58.5% (p<0.01). The parents of patients aged 5–7 years old noted the maximal shifts in PF - 66.2% (p<0.002), EF - 52.3% (p<0.001), in the overall assessment of QoL parameters - 65.4% (p<0.02) versus patients of the control group; the SF parameter was 76.8%, RF - 65.2%. Children and adolescents of 8–18 years old noted significant shifts towards the decrease of functioning in the social sphere - 89.3% (p<0.01), role activity - 70.7% (p<0.05), and the overall QoL assessment was decreased as well - 78.5% (p<0.05), PF parameter is 82.4%, EF - 69.3%. According to the opinion of parents of children aged 8–18 years old, the PF parameter is 71.0% (p<0.01), EF - 55.7% (p<0.002), SF - 77.1% (p<0.02), RF - 60.7% (p<0.01); the overall assessment of QoL parameters - 66.8% (p<0.005).

Conclusion: The decrease of all QoL parameters was reported in 57 children and adolescents with active celiac disease according to both parents' and children's opinion. Despite an impartial origin of QoL assessment, it should be noted that the used PedsQL questionnaire allows to reveal rather precisely the main types of functioning reflecting a slower physical development rate, psychoemotional disorders, and unavoidable difficulties in communicating with peers, which occurs very often in celiac disease.

Contact e-mail address: marina-stoyan@mail.ru
HLA-DQ2/DQ8 typing for non-biopsy diagnosis - is it necessary?

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Objectives and Study: Non-biopsy pathway for diagnosis of coeliac disease (CD) was implemented in the SW-England in May 2013. This requires anti-tissue transglutaminase (anti-tTG) titre >10-times the upper limit of normal (10xULN), positive anti Endomysial antibody (EMA) and positive HLA-DQ2/DQ8 haplotype. While the HLA-DQ2/DQ8 positive status in symptomatic children with anti-tTG >10xULN is considered necessary for non-biopsy diagnosis of CD, it has caused potential confusion and risk of misdiagnosis of CD if used inappropriately. This clinical study was set with the following objectives:

1. Identify the symptomatic paediatric patients in SW England diagnosed with CD via the non-biopsy pathway since May 2013.
2. Determine HLA-DQ2/DQ8 status in these patients
3. Final diagnosis when HLA DQ2/DQ8 was negative in these patients.
4. Feasibility of withdrawing HLA-DQ2/DQ8 testing from the non-biopsy pathway.

Subjects and Methods: Cases were identified from the electronic non-biopsy pathway register kept at the Bristol Royal Hospital for Children (BRHC) which was updated based on voluntary reporting of cases diagnosed serologically in BRHC and DGHs. The endoscopy register from BRHC was cross-checked for symptomatic cases with anti-tTG>10xULN but had negative HLA-DQ2/8.

Results: HLA-DQ2/DQ8 results were available for 96/110 patients. 95/96 patients (99.0%) were positive for HLA-DQ2/DQ8 (figure 5). Of these, 90/95 (94.7%) were HLA-DQ2 positive, 18/95 (18.9%) were HLA-DQ8 positive and 13/95 (13.7%) carried both haplotypes. For the remaining 14/110 patients, HLADQ2/DQ8 typing was not requested or not reported, but a diagnosis of CD was confirmed serologically nonetheless. One patient was negative for HLA-DQ2/DQ8, however subsequent small-bowel biopsy confirmed CD histologically of Marsh classification 3b.

Conclusion: We conclude that identification of the HLA DQ2/DQ8 status did not contribute towards confirming the CD diagnoses. Provided the high prevalence of HLA-DQ2/DQ8 in the general population, dangers of misuse and misinterpretations, alongside the significantly higher costs, we suggest consideration towards the removal of HLA-DQ2/DQ8 testing from the non-biopsy serological diagnostic criteria for CD. To clarify this further we propose a prospective national survey through the BSPGHAN to report HLA-DQ2/DQ8 negative cases in symptomatic children who are anti-tTG >10xULN and EMA positive.

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Dynamics of iron-deficient conditions in children with celiac disease on the background of gluten-free diet

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¹Stavropol State Medical University, Stavropol, Russian Federation
²Russian Medical Academy of Postgraduate Continuing Education, Moscow, Russian Federation

Objectives and Study: To analyze frequency of iron-deficient conditions (IDC): iron-deficiency anemia (IDA) and latent iron deficiency (LID) in children with celiac disease on the background of gluten-free diet (GFD) and to compare the parameters in compliant and non-compliant patients.

Method: 70 children and adolescents aged 3 to 17 years old with celiac disease including 31 (44.3%) boys and 39 (55.7%) girls; the diagnosis was made in accordance with the ESPGHAN clinical laboratory and morphological criteria (1990, 2012). The patients were divided in 2 groups depending on diet compliance: 51 (72.9%) compliant and 19 (27.1%) non-compliant with GFD. The analysis of ID dynamics in the compliant group was performed after 6 m (28 subjects), 12 m (29 subjects), 24 m (21 subjects), 36 m (21 subjects), 48 m (16 subjects), 60 m (8 subjects)

Results: The total frequency of IDC in children during the CD diagnosis verification period was 61.4%; 22 (31.4%) of the CD patients were diagnosed with IDA and 21 (30.0%) children were diagnosed with LID. During the first 6 months of GFD compliance, IDA is completely arrested in patients with CD; after 12 months the IDA frequency is 10.3% (p&LT; 0.05), after 24 and 36 months - 9.5% (p&LT; 0.05) in both cases. After 48 months of GFD compliance, the IDA frequency is increased up to 25.0%, and after 60 months it can be reduced to 12.5% again. The LID frequency on the background of strict GFD compliance slightly differs: after 6 months it is not changed significantly being 32.1%; after 12 months it is reduced to 24.2%; after 24 and 36 months - 23.8% in both cases; after 48 and 60 months it is reduced 2.4 times if compared to the baseline level: from 30.0% to 12.5%. GFD noncompliance led to an increase in IDC frequency up to 68.4%, mainly due to IDA which was diagnosed in 36.8% of patients; LID was diagnosed in 31.6% of children. The average Hb level in patients with acute celiac disease was 116.1±2.1 g/l, and BI - 9.8±0.6 µmol/l. On the background of GFD, the Hb level is increased and as early as after 6 months it is within the reference range in most children. After 60 months of GFD the average Hb level is 129.9±4.3 g/l (p&LT; 0.01), and in case of GFD noncompliance - 119.1±3.6 g/l. The average BI is increased rather rapidly being 12.8±0.9 µmol/l even after 6 months of GFD (p&LT; 0.01), and it remains within the normal range during all the years of follow up; meanwhile it is decreased to 9.1±1.0 µmol/l (p&LT; 0.05) in non-compliant patients

Conclusion:
1. Strict GFD compliance by patients with CD leads to a significant decrease in the number of children with IDC. The frequency of IDA on the background of GFD is reduced 2.5-3.3 times and the frequency of LID - up to 2.4 times in compliant patients.
2. The absence of GFD compliance leads to preservation of IDC whose frequency is about 70.0%; meanwhile preservation of anemia is a rather sensitive laboratory criterion showing the absence of clinical laboratory remission of CD
3. The average Hb and BI levels in children, compliant with GFD, clearly increase getting as high as the average values in children of the corresponding age. If GFD is not observed, a drop in hematologic parameters is noted if compared to the baseline data
4. In case of clinical and laboratory signs of ID, iron therapy is recommended to patients with CD who observe GFD

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**Objectives and Study:** Gluten-free diet (GFD) is the only available treatment for celiac disease (CD). The nutritional adequacy of GFD has been long a debated issue, however few nutritional studies have been performed so far. The present study aimed to evaluate the nutritional status and dietary intake of CD affected children on a GFD as compared with non-celiac children and with Italian nutritional intakes recommendations.

**Method:** This is a case-control observational study conducted at the Department of Pediatrics of Marche Polytechnic University (Italy) from January to December 2017. All CD children with a biopsy-proven diagnosis of CD on a GFD for at least 2 years and a sex and age-matched control group of healthy children were recruited. The nutritional status of both groups was evaluated by clinical (body mass index) and lifestyle assessment (level of physical activity and prolonged sitting time activities) and by dietary intakes collected using a prospective 3-days food frequency questionnaire. Nutritional intakes were compared between the group and controls and with Italian dietary reference values.

**Results:** Fifty celiac children (female 70%, median age 11.1 years, median GFD duration 4.3 years), and 50 non-celiac controls (female 60%, median age 10.8 years) were enrolled completed the study. There was no significant difference between CD children and control group in clinical parameter (median body mass index: CD 18.2 vs control group 16.3; p=0.7) and level of physical activity (4 hours/week) and sitting time activities (2 hours/day). Median energy intake was similar in CD patients and controls (1731.1 kcal and 1836.4 kcal; p=0.2). Protein, carbohydrate and fat-derived energy and intake of fibers did not differ between the two groups. Both children groups showed higher carbohydrate and lower fibers intakes than recommended.

**Conclusion:** Nutritional status, level of physical activity and dietary intake patterns are comparable between CD children and controls. Intakes of simple sugars and intake of fibers does not follow the National recommendations for health in both groups. Dietitians should take the opportunity to reinforce a generally healthy diet when providing information about the GFD.

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Macronutrient dietary composition in children and adolescents with Type 1 Diabetes and Coeliac Disease: the impact of processed gluten-free food

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2Pediatric Diabetes and Metabolic Disorders Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Objectives and Study: To evaluate the differences of macronutrients dietary composition in children and adolescents with coexisting Type 1 Diabetes (T1D) and Coeliac Disease (CD) on mainly naturally gluten-free diet (NGFD) or processed gluten-free diet (PGFD). To evaluate the effects of macronutrients dietary composition on anthropometric and metabolic parameters.

Method: Thirty-two children/adolescents with coexisting T1D and CD (age range 5-18 years) were enrolled. Diet (3-day weighed dietary record), physical (height, weight, waist circumference, bioelectrical impedance analysis) and biochemical (HbA1c, lipid profile) parameters were recorded. PGFD was defined as a diet with more of 50% of kcal from industrial gluten-free foods. Relationships between variables were assessed by Pearson correlation coefficients and a multiple regression analysis, using non-HDL cholesterol, a gross index of cardiovascular disease (CVD) risk, as dependent variable, was also run.

Results: Percentage of kcal from processed gluten-free foods was significantly associated with age (r = -0.46, p< 0.01), duration of T1D (r = -0.38, p< 0.05), duration of CD (r = -0.35, p< 0.05). Moreover, it was positively associated with carbohydrate (CHO) intake of the diet (% EI; r = 0.52, p< 0.01) and negatively associated with lipid intake of the diet (% EI; r = -0.37, p< 0.05); No statistically significant association with glycometabolic control (HbA1c) was found. Excluding the effect of age, duration of T1D and duration of CD, a statistically significant association was found between the percentage of CHO intake of the diet and non-HDL cholesterol (r=-0.48; p< 0.01) (Figure 1). Multiple regression analysis showed that percentage of CHO intake of the diet explained about the 16% of inter-individual variability of non-HDL cholesterol independently from age, duration of T1D, duration of CD and percentage of kcal from processed gluten-free foods.
**Conclusion:** Gluten-free diet with a higher content of processed gluten-free food has a composition higher in CHO and lower in lipids, which is closer to nutrition guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD).

A pro-atherogenic index (non-HDL cholesterol) is associated with diet composition in this population: a higher level of CHO in the diet composition seems to play a positive role in determining a better lipid profile with a potentially lower CVD risk. Although a mainly naturally gluten-free diet is likewise recommended, a specific nutrition education to patients with T1D and CD and their families need to be implemented to balance macronutrients composition of the diet and to prevent above-mentioned lipid profile alterations.

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Clinical presentation of coeliac disease in children and adolescents from Central European region in 2016

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Objectives and Study: Coeliac disease (CD) is a lifelong immune-mediated systemic disorder, affecting genetically susceptible individuals after ingestion of gluten. It occurs approximately in 1% of the population and has diverse clinical presentation, ranging from classical gastrointestinal manifestation of malabsorption to subclinical and asymptomatic forms. The aim of our study was to present clinical manifestations of CD among the children and adolescents in Central European (CE) region.

Method: 41 centres from five CE countries (Croatia (CRO) 6, Germany (GER) 5, Hungary (HUN) 21, Italy (ITA) 2 and Slovenia (SLO) 7) provided data as a part of a multi-centre web-based survey. We retrospectively analysed medical records of children and adolescents diagnosed with CD in 2016, focusing on a single leading symptom indicative of CD and other associated symptoms. We compared clinical presentation at the time of diagnosis of preschool (< 6y) and school-age children and analysed regional differences in clinical picture. Statistical analysis was performed using SPSS for Windows.

Results: Data from 652 children and adolescents (64.0% female, 37.0% preschool) from CRO (N=66), GER (N=69), HUN (N=381), ITA (N=82) and SLO (N=54) with the diagnosis of CD, confirmed in 2016, were available for further analysis. Median age at the time of diagnosis was 7 years (range 7m-18.5y). 20.2% of children were asymptomatic, out of which 64.4% belonged to a known risk group (73% with positive family history of CD).

The most common leading symptom at the time of diagnosis was abdominal pain (33.1%), followed by growth retardation[1] (13.8%) and diarrhoea (12.9%). We did not find any regional differences regarding the most common leading symptom. Abdominal pain was also found to be the most common leading symptom in both, preschool (20.9%) and school-age (41.1%) children. In preschool children, the second most common leading symptom was diarrhoea (17.0%), followed by growth retardation (16.0%) and in school-age children the opposite was found (growth retardation - 12.4%, diarrhoea - 10.2%). Considering all the symptoms (leading symptom and other associated symptoms) abdominal pain was again the most frequent one (51.5%), followed by abdominal distention (32.1%) and diarrhoea (30.6%).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>TOTAL (N=652)</th>
<th>CROATIA (N=66)</th>
<th>GERMANY (N=69)</th>
<th>HUNGARY (N=381)</th>
<th>ITALY (N=82)</th>
<th>SLOVENIA (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic CD</td>
<td>20.2%</td>
<td>12.1%</td>
<td>23.2%</td>
<td>20.7%</td>
<td>24.4%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Abdominal pain as a lead symptom</td>
<td>33.1% (51.5%)</td>
<td>36.4% (47.0%)</td>
<td>36.2% (56.5%)</td>
<td>24.4% (41.2%)</td>
<td>14.6% (23.2%)</td>
<td>33.3% (40.7%)</td>
</tr>
<tr>
<td>Symptom</td>
<td>(as all symptoms)</td>
<td>(as all symptoms)</td>
<td>(as all symptoms)</td>
<td>(as all symptoms)</td>
<td>(as all symptoms)</td>
<td>(as all symptoms)</td>
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</tr>
<tr>
<td><strong>Growth retardation</strong></td>
<td>13.8% (21.9%)</td>
<td>9.1% (16.7%)</td>
<td>17.4% (18.8%)</td>
<td>10.5% (17.8%)</td>
<td>13.4% (19.5%)</td>
<td>5.6% (11.1%)</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>12.9% (30.6%)</td>
<td>15.2% (25.8%)</td>
<td>4.3% (27.5%)</td>
<td>10.2% (23.9%)</td>
<td>12.2% (24.4%)</td>
<td>9.3% (22.2%)</td>
</tr>
<tr>
<td><strong>Iron deficiency</strong></td>
<td>10.2% (24.0%)</td>
<td>7.6% (15.2%)</td>
<td>2.9% (4.3%)</td>
<td>9.4% (24.9%)</td>
<td>6.1% (11.0%)</td>
<td>9.3% (14.8%)</td>
</tr>
<tr>
<td><strong>Abdominal distention</strong></td>
<td>7.1% (32.1%)</td>
<td>3.0% (9.7%)</td>
<td>5.8% (20.3%)</td>
<td>6.6% (31.5%)</td>
<td>3.7% (11.0)</td>
<td>5.6% (20.4%)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>5.4% (13.8%)</td>
<td>3.0% (9.1%)</td>
<td>1.4% (5.8%)</td>
<td>3.9% (9.4%)</td>
<td>7.3% (19.5%)</td>
<td>7.4% (18.5%)</td>
</tr>
<tr>
<td><strong>Unexplained fatigue</strong></td>
<td>3.3% (11.7%)</td>
<td>1.5% (9.1%)</td>
<td>4.3% (14.5%)</td>
<td>2.4% (6.8%)</td>
<td>4.9% (14.6%)</td>
<td>0.0% (13.0%)</td>
</tr>
<tr>
<td><strong>Other symptoms</strong></td>
<td>4.0% (4.2%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>4.7% (5.0%)</td>
<td>3.7% (3.7%)</td>
<td>0.0% (0.0%)</td>
</tr>
</tbody>
</table>

[**Clinical presentation of CD in CE regions.**]

**Conclusion:** Our data showed that clinical presentation of CD is diverse in children in CE. Although classical clinical presentation is not so frequent, gastrointestinal symptoms, especially abdominal pain, remain the leading symptom in all groups of children and adolescents. In school-age children, abdominal pain was twice as common as in preschool children. In Germany it was a leading complaint in almost half of the children.
Also becoming increasingly common is for CD to present as an asymptomatic disease. Our data showed that one fifth of included children had no symptoms before the diagnosis with asymptomatic group being the largest in Italy and Germany compared to the other regions.
It is very important to raise the awareness about the changes in clinical presentation of childhood CD shown by our data and by other studies in order to prevent diagnostic delays and negative consequences of undetected/untreated disease.

*Study was co-financed by Interreg CE programme (CE 111, Focus IN CD).*

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Antibodies against neo-epitope of microbial and human transglutaminases in paediatric coeliac disease

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Objectives and Study: Microbial transglutaminase (mTg) and human tissue Tg (tTg) form complexes with gliadin peptides, thus posttranslational modifying gliadin, changing physical-chemical features and 3D confirmation, exposing neo-epitopes. The aims were to test the diagnostic performance of those antibodies against both non-complexed and complexed forms of both transglutaminases in children with coeliac disease, compared with disease controls and to correlate antibodies’ levels to the degree of intestinal atrophy.

Method: Serum samples, at day of intestinal biopsy, were collected from 350 children with coeliac disease (mean age 7.4 years) and 215 disease controls (mean age 10.2 years) and tested using the following ELISAs detecting IgA, IgG or both IgA+IgG combined (Check): tTG (for in house research use only), AESKULISA® tTg New Generation (tTg neo-epitope (tTg-neo)) and mTg neo-epitope (mTg-neo, RUO). Results were correlated to the degree of intestinal injury, using the revised Marsh criteria.

Results: mTg-neo Check had the highest sensitivity and tTg IgA the highest specificity. Comparing the different correlations between antibodies’ isotypes, the tTg Check ($r=0.7889$, p<0.0001) and tTg-neo Check ($r=0.7544$, p<0.0001) as well as tTg IgA and tTg-neo IgA ($r=0.7571$ and $r=0.7279$, p<0.0001 respectively) were the best indicators of intestinal damage in CD.

Conclusion: It is suggested that the combination of tTg-neo IgA/IgG antibodies should be recommended as a first line screening test for coeliac disease in children. The tTg and tTg-neo assays show similar diagnostic performance and are recommended as good screening tests for coeliac disease in children. mTg-neo IgG presents a new serological biomarker for coeliac disease.

Disclosure of interest: The presenting author is the CEO of the company.
Menarcheal age is not delayed in patients with coeliac disease in Slovenia

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Objectives and Study: Coeliac disease is an autoimmune disorder associated with numerous health problems due to malabsorption. It is primarily a gastrointestinal disease characterized by intestinal mucosal damage, however, it is not limited to the gut and may even affect reproductive health of the individual. Reproductive changes have been described including delayed onset of menarche, amenorrhea, recurrent abortions, reduced rates of pregnancy as well as adverse outcomes in pregnancy and the postpartum period that may lead to miscarriages and premature low birth weight fetal deliveries. All this can be possibly related to the immune-mediated mechanisms or nutrient deficiency.

The aim of the present study was to analyze the reproductive health indicators, particularly menarche age and characteristics of menstrual cycle, in the group of coeliac patients in comparison to the data obtained from National Health Survey in Europe and Slovenia.

Method: The retrospective study included 145 patients with coeliac disease, members of Slovenian Celiac Society, between 15 and 50 years. Age at menarche as well as characteristics of the menstruation were obtained with a questionnaire developed for the study. For statistical purposes the data were submitted to analysis of variance (ANOVA). Data are expressed as mean ±SD, median, and range. Differences were considered statistically significant at p< 0.05.

Results: Results showed that 84.3% the female coeliac patients reported onset of menarche between 11 and 15 years, 11.9% after 15 years and 3.8% before 11 years. The mean age at menarche was 12.7 years. For majority of patients the length of menstrual cycle was around 27-28 days with 4-5 days of bleeding. Furthermore, 33% of patients experienced bleeding between the cycles. 51% of patients reported having painful periods and for that reason 24% of them regularly take medications. Furthermore, only 2% of patients involved in the study were treated for amenorrhea. The results revealed that 71.7% of participants in the study started with gluten free diet (GFD) after 18 years, 16.5% between 6 and 18 years, 4.8% between 2 and 6 years while 7% already before 2 years of age.

<table>
<thead>
<tr>
<th>Age of menarche (y)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>11-15</td>
<td>123 (84.3%)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>17 (11.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The onset of gluten free diet.</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>10 (7)</td>
</tr>
<tr>
<td>2-6</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>6-18</td>
<td>24 (16.5)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>104 (71.7)</td>
</tr>
</tbody>
</table>

Conclusion: Based on our results we conclude that menarche age is not delayed in patients with coeliac disease. The onset of menarche in coeliac disease patients is comparable to the reported data for female population of National Health Survey in both Slovenia and other European countries, which is between 11 and 15 years.

Taking into account that menarche age is often reported to be delayed in patients suffering from chronic diseases our findings might be encouraging suggesting that age of diagnosing coeliac disease and start of gluten free diet may not play an important role in conditioning menarcheal age in coeliac patients.
Keywords: children, celiac disease, menarche age, menstrual disturbances.

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Circulating antibodies against osteoprotegerin in children with celiac disease

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Background and Aim: Evidences indicate that a low bone mineral density (BMD) could be found in 20-50% of newly diagnosed patients with celiac disease (CD). Neutralizing auto-antibodies against osteoprotegerin (Ab-OPG) have been recently shown in the sera of untreated CD patients, suggesting that blocking the inhibitory effect on osteoclasts may have a role in bone damage in these patients. This study aimed to investigate the presence of circulating auto-antibodies against OPG in pediatric CD patients with and without villous atrophy (potential CD).

Methods: We tested sera from 33 CD patients (16 with active disease and villous atrophy-GCD; 17 remission on a gluten-free diet-GFD), 48 potential CD (PCD), who also underwent bone metabolism evaluation, albumin, calcium, phosphate, alkaline phosphatase and vit D + BMD analysis, and 28 healthy controls (CTL), matched for sex and age. For the immunoprecipitation assay, serum samples were incubated at a 1:100 dilution with 12.5 ng of homodimeric recombinant human osteoprotegerin and tested by western blotting with an anti-OPG antibody. A direct enzyme-linked immunosorbent assay (ELISA) was also developed and used to screen the same patients for autoantibodies to OPG.

Results: Western blotting showed presence of Ab-OPG in 62.5% in GCD (10/16), in 18.75% GFD (3/16), 17.85% in CTR (5/28) and in 12.5% (6/48) PCD. Statistically analysis was significant only in GCD compare to CTR (p=0.002). Same results have been obtained also with ELISA, except that we observed a statistically significant difference among POT and CTR (p=0.03). 34/48 patients with PCD underwent also a BMD analysis and 12/34 (35.3%) showed a low BMD (Z score -2.65), but no alteration in any other parameters of bone metabolism (albumin, calcium, phosphate, alkaline phosphatase and vit D). No correlation between low BMD and presence of antibodies against OPG in the serum have been found. 5/12 of these patients were put on a gluten free-diet for more than 2 years, but no benefits on BMD have been proved compared to those that were still on a gluten containing diet.

Conclusion: In our pediatric CD cohort, antibodies against OPG are specifically present in the serum of active patients and decreased after gluten free diet. No correlation has been showed in PCD between the presence of ab-OPG in the serum and bone metabolism alterations and no benefits after gluten free diet. These data suggested that other mechanisms should be involved in bone metabolism in PCD.

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Group sessions are a good medium for educating patients with coeliac disease

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Objectives and Study: To assess the impact of educating children and their families on the gluten free diet in a group session.

Prior to March 2016 all newly diagnosed coeliac patients referred to dietetics in Birmingham Children’s Hospital were given a 30 minute slot in the dietetic gastroenterology clinic. Finding extra clinic slots for the increasing number of children being referred was difficult so group sessions were introduced in March 2016. Until October 2017 6 families were invited to the group session and from November 2017 the number increased to 10 families.

Methods: Children with behavioral or learning difficulties or with parents who need an interpreter are excluded. These patients are offered a standard clinic appointment. The group session invitation advises parents that they are attending a group session and asks them to contact us if they do not consent to the group session. These patients will also be offered a standard clinic appointment.

Group sessions are held monthly and last for 1.5 hours. They are run by a dietitian with the support of a dietetic assistant. A room is used that can hold at least 30 people so children can bring additional members of their family who may be involved in food provision such as grandparents.

A standardised presentation devised from the Dr Schär® Institute presentation teaching pack is used. This includes endoscopy pictures and we added useful apps to demonstrate in the session which helps engage the teenage children. Parents are asked to add their own practical knowledge and active discussions are encouraged between families.

At each session the dietetic assistant supervises the younger children and gives them a picture specially designed by our medical illustrations department that contains gluten and non-gluten containing food for them to colour in during the session. She also works with them to create a plate of their favourite food and discusses gluten free alternatives with them.

Results: Until November 2017 83 children have attended the sessions. The practical session allows the children to learn in a fun way so their parents can focus on the dietitian’s presentation. Parents can exchange contact details with other parents for support and the children can meet others with their condition. We have had very positive feedback such as “we wish we’d had this when she was diagnosed”, they felt the dietitian was very knowledgeable and they enjoyed the session.

Conclusions: The group sessions are an effective medium for educating children and their families on the gluten free diet and the experience of attending the session is a much better experience for the child. The dietetic assistant role allows parents to focus on the session by preventing the younger children from becoming bored whilst assisting with their dietary education in the medium that suits them best.

There are health economics benefits of the group session because they have a 1.5 hour session rather than 30 minutes session. Offering 6 places per month increased our capacity by 100% and 10 places increased our capacity by 233% without increasing the frequency of our clinic sessions.

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Markers able to predict progression towards small villous atrophy in patients with potential coeliac disease

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²Azienda Universitaria Ruggi D’Aragona, Castel San Giorgio, Italy

Objectives and Study: Today 20% of celiac diagnosis are defined as potential celiac disease (PCD). This condition is characterized by the absence of small villous atrophy despite the presence of positive celiac specific antibodies in patients carrying HLA DQ2 and/or DQ8 haplotype. The aim of our study was to identify markers able to predict the progression towards acute celiac disease (CD) and to define guidelines for the clinical management of PCD.

Method: We recruited 39 patients (mean age: 16.6 yrs), who received diagnosis of PCD from 2007 to 2010. When discharged from our celiac centre 4/39 patients began a gluten-free diet and were subsequently challenged, while 35/39 continued to assume gluten normally. Depending on the course of CD specific serology PCD patients were classified in serologically persistent (group A n=13), negative (group B n=15) and fluctuant (group C n=11). From 2010 to 2017 patients underwent clinical and laboratory assessment. Biopsies were performed in case of positive EMA and/or anti TG2 or in the presence of malabsorption symptoms.

Results: During the follow-up we observed that in group A all patients (13/13) remained serologically positive, in group B 14/15 patients remained negative and 1/15 returned to be positive, while in group C most patients became negative (7/11), one developed a positive serology and 3/11 continued to have fluctuant levels of CD specific antibodies. CD developed in 17/39 (44%) patients (13 of group A, 1 of group B and 3 of group C). Interestingly, only 2/4 patients that were re-exposed developed CD. In 22/39 (56%) patients, still on a normal gluten intake, we compared between 2010 and 2017 BMI, hemoglobin and ferritin levels and fecal calprotectin. We didn’t observe any worsening. Moreover, in two patients, because of the presence of malabsorption symptoms, even in the absence of CD specific antibodies, we performed a small intestinal biopsy, which revealed to be Marsh 0.

In order to identify markers able to predict progression towards acute CD, we compared in our cohort patients who developed small villous atrophy (CD group) with patients who remained in a potential condition (PCD group). We observed that progression towards small villous atrophy was significantly influenced by the presence in the CD group of high risk HLA alleles (DQ2-DQ2) (41% versus 4%), the presence of lymphocyte infiltration (Marsh 1) (47% vs 9%), the persistence of serum celiac specific antibodies (76% vs 4%) and the presence of CD in the familial history (41% vs 28%). Considering symptoms, we observed in the PCD group a higher prevalence of asymptomatic patients (40% vs 11%).

Conclusion: We conclude that PCD patients can be subdivided in different class risks considering serology, HLA, Marsh lesion and familial history. In high risk patients we propose a more strict follow-up including further biopsies. Patients on a gluten-free diet need to be re-exposed. Our clinical data in line with immunological data indicate that PCD patients with Marsh 0 lesion might represent a new clinical, immunological and perhaps genetic condition not necessarily preceding acute CD. However, the short period of observation cannot exclude complications in the future.
Nutritional and clinical assessment in patients with PCD on a normal diet from 2010-2017

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Gastroenterology - Coeliac Disease

G-P-050

Spectrum of liver involvement in Celiac Disease

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Objectives and Study: Liver involvement in children with Celiac disease (CD) may vary from asymptomatic celiac hepatitis to chronic liver disease in the setting of autoimmunity. The present study was aimed to study the spectrum of hepatic involvement in children with CD and to correlate the severity of hepatic involvement with intestinal disease.

Method: All children under-18 years of CD diagnosed as per ESPGHAN guidelines were enrolled. Liver involvement was studied in patients in terms of elevation of transaminases (>25.8U/L for boys, and >22.1U/L for girls), and/or clinical, sonographic or histological evidence of chronic liver disease and/or portal hypertension.

Results: 115 (72 males) children with CD were identified out of which 37 were potential CD. Elevation of transaminases was seen in 64 (55.6%) children - of these 46 had celiac hepatitis, 16 had autoimmune liver disease (autoimmune hepatitis in 13, autoimmune sclerosing cholangitis in 2 and primary sclerosing cholangitis in 1) and 2 patients had hepatic venous outflow tract obstruction (HVOTO) based on liver biopsy findings. Liver biopsy available in 22 children showed features compatible with autoimmune liver disease in 11, steatohepatitis in 06 , and chronic hepatitis in 04 . One of the child had hepatocellular carcinoma in the setting of HVOTO. There was no significant correlation seen between the levels of transaminases with that of tTG or with the degree of villous atrophy. Out of the 20 patients with Celiac Hepatitis who were on regular follow up, 14 showed resolution of transaminases over a period of 4-6 months.

Conclusion: More than half of the patients with Celiac Disease have liver involvement. The spectrum of liver involvement in these patients is wide, however there is no correlation with the severity of intestinal disease.

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The uptake and effectiveness of serology based confirmation of coeliac disease in children in a large tertiary UK centre

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Objective: ESPGHAN published guidelines in January 2012 allowing for confirmation of the diagnosis of coeliac disease (CD) without histological analysis of small bowel mucosa biopsies in symptomatic children with high levels of circulating tissue transglutaminase antibodies (TTG), anti-endomysial antibodies (EMA) and positivity of HLA-DQ2 or DQ8. This study assessed the usage and effectiveness of these guidelines in a tertiary paediatric gastroenterology centre.

Methods: A retrospective review of all children (age < 18 yrs at presentation) newly diagnosed with CD at King's College Hospital (KCH) from 1/2/2012 to 31/12/2016 with 1 year follow up data available. If endoscopy was performed, 2 biopsies were taken from the duodenal cap and 4 from D2 or lower, as per protocol. Histology was analysed using the modified Marsh grading system. Data were collected using electronic patient records. Analysis was performed using SPSS version 21 (Chicago, USA). Significance was defined as p< 0.05.

Results: 82 patients were newly diagnosed with CD during the study period. 12 were asymptomatic patients identified via screening and so were excluded from further analysis. 70 symptomatic children were diagnosed. 61% (n=43) were female. The median age at diagnosis was 7.58 yrs (Range 0.86 - 17.66). The commonest presenting symptom was abdominal pain, with over 50% of patients affected. All patients had TTG measured at baseline, with a mean[SD] of 88.0[46.6] U/ml, 7 being the upper limit of normal (ULN) and 128 the maximum recorded with our assay. 35.7% (n=25) of this cohort had a TTG < 10 times ULN. These patients all underwent endoscopy, as per ESPGHAN guidelines. Overall, 76% (n=53) were diagnosed by endoscopy and biopsy. No patients had concomitant pathology diagnosed and there were no operative complications. 47% (n=33) had complete serological testing performed, and 34% (n=24) fulfilled ESPGHAN serological diagnostic criteria. 24% (n=17) were given a diagnosis of CD without proceeding to endoscopy and small bowel biopsies. 75% of patients (n=18) who met the criteria were offered non-biopsy diagnosis and all but one preferred this option. A summary of the diagnostic process is shown in Figure 1. At maximum follow up, none of the patients diagnosed serologically have required endoscopy.
There was a significant fall in TTG from baseline (mean 87.3, SD 46.5) at 6 months (mean 23.5, SD 29.7; p=0.003) and at 12 months (mean 12.5, SD 22.1; p=0.017). The decrease in TTG was significantly greater in children diagnosed serologically both at 6 months (mean [SD] 82.8 [42.0] vs 57.6 [43.6]; p=0.04), and at 12 months (mean [SD] 93.0 [41.2] vs 67.4 [45.6]; p=0.049).

**Conclusion:** Serology based confirmation of CD proved to be both effective and appealing to our patient population and the results should encourage greater uptake of this diagnostic strategy. Small bowel biopsies remain important in children with suggestive symptoms but whose TTG titres are $< 10$.
times the ULN, or in whom there is concern about dual pathology.

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Diagnostic delays in children with coeliac disease in the central european region in 2016

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Objectives and Study: Coeliac disease (CD) is a lifelong immune-mediated systemic disorder affecting about 1% of the population. The majority of adult and paediatric patients remain undiagnosed and diagnostic delays in many regions reach up to 10 years. The aim of our study was to identify the diagnostic delays in children with CD in Central European region.

Method: We retrospectively analysed medical records of children and adolescents diagnosed with CD in 2016 from five Central European countries as a part of a multi-centre web-based survey, focusing on the age at the diagnosis and the duration between first CD related symptoms, first visit to paediatric gastroenterologist and confirmation of the diagnosis. Differences between preschool (< 6y) and school-age children were also studied. Statistical analysis was performed using SPSS for Windows.

Results: Data from 459 children and adolescents (66% female, 41% preschool) from Croatia, Hungary, Germany, Italy and Slovenia, were available for further analysis. Median age at the time of diagnosis was 7 years (range 7m-18.5y) and more than two thirds of children were diagnosed before the age of 10 years. There was significant difference between regions regarding the median age at the diagnosis, being the lowest in Italy, and the highest in Croatia (p< 0.05).

Median duration from first CD related symptoms to the first visit of paediatric gastroenterologist was 6 months (range 0-14y; preschool 5m (0-5y), school-age 6m (0-14y)), with no significant regional difference.

Median duration from the first visit of paediatric gastroenterologist to the confirmation of the diagnosis was 1 month (range 0-8y; preschool 1m (0-8m), school-age 1m (0-8y)) and significant difference was found between regions (p< 0.001), being the highest in Croatia and Slovenia.

Median delay from the first symptoms to diagnosis was 8 months (range 0-14y; preschool 6m (0-5y), school-age 9m (0-14y)) without difference between regions.
Conclusion: Our data showed that diagnostic delays in children with CD in five Central European countries are lower in comparison with the available data from other regions. Within the Central Europe, we did not find important differences in delays between the onset of symptoms and final diagnosis. However, the delay between the first visit of paediatric gastroenterologist and the final diagnosis was significantly higher in Slovenia and Croatia. This could be attributed to regional differences in the availability of diagnostic methods and/or capacity of paediatric gastroenterology service, as well as to the older age at diagnosis in Slovenia and Croatia, which is correlated with longer diagnostic delays, however it also could be caused by lower number of patients from some countries.

Regardless of relatively short diagnostic delays that we found, there is still a room for further improvement. Undiagnosed and/or untreated CD is associated with severe complications; therefore, it is very important to raise the awareness about the disease prevalence, changes in clinical presentation, and the use of reliable diagnostic methods in order to further reduce delays and the unnecessary burden of undetected and thus untreated disease.

*Study was co-financed by Interreg CE programme (CE 111, Focus IN CD).

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Gluten-related disorders in paediatric dermatology department

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Objectives and Study: In the department of dermatology in our hospital, about 60% of patients are with atopic dermatitis, about 30% with various forms of psoriasis; and other patients with rare forms of dermatitis, such as epidermolysis bullosa. Among these patients, gluten-related disorders, such as asymptomatic celiac disease (CD) and dermatitis herpetiformis, have often become revealed. The aim of our study was to find out how often gluten-associated disorders can be found among pediatric dermatology patients.

Method: Patients with atopic dermatitis, as well as dermatitis of unidentified etiology and alopecia, were tested for antibodies to tissue transglutaminase-2 IgA, IgG by immunoferment assay (Orgentec, Germany), when positive, gastroscopy with duodenal biopsies and histological and immunohistochemical study to determine the amount of CD3+ interepithelial lymphocytes, as well as HLA-typing (PCR) to determine the haplotypes DQ2, DQ8 were done. Nutritional status was assessed by the WHOAnthroPlus program (Z-score Body Mass Index for Age, BAZ; Weight for Age, WAZ; Height for age, HAZ).

Results: We had 1576 dermatologic patients in 2015-2017. The diagnosis of CD was confirmed in 14 children aged 3.5 to 17 years, which was 0.9% of the total number of patients and 1.6% of patients referred to us with a diagnosis of atopic dermatitis. All these children received ineffective treatment for atopic dermatitis for a long time. Five patients had total alopecia or alopecia areata; in 4 the diagnosis of dermatitis herpetiformis (confirmed histologically) was established, the rest had celiac disease combined with atopic dermatitis. Low- or asymptomatic course of celiac disease in our patients should be noted: only 1 girl was malnourished (WAZ -2.45 HAZ -2.42 BAZ -1.16); gastrointestinal symptoms were rare and mild (inconstant stool in 4, abdominal distension in 3, abdominal pain in 4). Deficient symptoms were observed rarely also: mild anemia in 3 (Hb 102-105 g/l), enamel defects in 4 patients. A significant increase in total IgE (745-3000 U/l) was found in only 3 patients with atopic dermatitis. All children with atopic dermatitis and dermatitis herpetiformis had pronounced positive effect of gluten-free diet with significant decrease or disappearance of skin rash and pruritus, improvement of well-being; beginning of hair growth in 2 children with alopecia areata after 3-6 months of diet.

Conclusion: Although the detected incidence of CD in our dermatological department is not so high compared to the global figures, we consider it necessary to perform screening (antibodies to tissue transglutaminase) among patients with poorly treatable atopic dermatitis, all types of atypical dermatitis and alopecia, since a gluten-free diet in case of revealed CD is extremely effective in relation to the skin process.

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Compliance to GFD in children with coeliac disease and factors affecting dietary compliance during childhood

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Objectives and Study: Coeliac disease is an autoimmune, inflammatory enteropathy that is caused by ingestion of dietary gluten found in grain products. Lifelong strict gluten free diet (GFD) is the only known effective treatment not only to control symptoms but also to improve quality of life and decrease the risk of complications. Strict adherence to GFD may be more challenging in children than in adults. Since noncompliance is a major problem and a big challenge for the physicians who treat children with CD, factors affecting compliance to GFD and predictors of compliance to GFD in children have been a matter of utmost importance. The aim of this study was to evaluate the compliance to GFD and to find out the factors, which may predict non-adherence to GFD in children.

Method: This cross-sectional study enrolled 100 children with biopsy confirmed coeliac disease who were ≤18 years of age. Adherence to GFD was assessed by measuring serum tTG antibodies. Furthermore, a questionnaire addressed to the parents was applied to assess the factors, which may affect the compliance to GFD.

Results: At recruitment, the mean age of the study group was 12.2 ± 4.9 years and 65% were female. The median elapsed time after the diagnosis was 4 years (mean 4.8 ± 4 years, range 1-16 years) and 41% of patients had been followed for at least 5 years. The mean age at diagnosis was 7.4 ± 3 years. Adherence to GFD in this cohort was 55%. There was no difference between the compliant and non-compliant groups in terms of the age at diagnosis or gender. However, the current mean age was higher and the mean elapsed time since the diagnosis was longer in non-compliant group compared to the compliant group. Dietary adherence in coeliac children who presented with atypical symptoms was poorer than the patients presented with typical malabsorptive symptoms. Household crowding and lower socioeconomic status were associated with poor compliance whereas there was not any difference between the compliant and non-compliant groups in terms of maternal education. More than half (55%) of the parent was not aware of the inadvertent gluten ingestion through gluten cross-contamination in this cohort. On top of that, 44% of parents reported difficulties in acquisition of gluten free products, and 95% of parents declared that gluten free products are very expensive.

Conclusion: Although GFD is the sole treatment for coeliac disease, dietary adherence is rather low in childhood. Inadequate education and socio-economic handicaps are important determinants of poor dietary compliance. Improvement of these handicaps and better dietary instructions may contribute not only to dietary adherence but also to prevention of long-term complications.
Diagnosis of coeliac disease in asymptomatic patients: Applicability of espghan guidelines "biopsy-sparing"

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Objectives and Study: In 2012 European Society of Paediatric Gastroenterology, Hepatology, and Nutrition published novel guidelines on coeliac disease (CD) diagnosis. Symptomatic children with serum anti-transglutaminase (anti-tTG) antibody levels ≥10 times upper limit of normal (ULN) could avoid duodenal biopsies after positive HLA test and serum anti-endomysial antibodies (EMAs). So far, both asymptomatic and symptomatic patients with anti-tTG titer < 10 times ULN should undergo upper endoscopy with duodenal biopsies to confirm diagnosis. The aim of this study is to assess the applicability of current biopsy sparing guidelines also among children and adolescents non fulfilling the “non biopsy” criteria, thus reducing the costs and risk associated with the procedure and sedation.

Method: We retrospectively reviewed data of 398 patients from January 2012 until December 2016: age M 7,2 years (range 9 months 20 years). A group of 51 patients was diagnosed according to the 2012 non-bioptic ESPGHAN criteria (not included in the study). A second group of 347 patients had a CD diagnosis based on elevated titer of anti-tTG, EMA positivity and histology. Histological lesions were graded according to the Marsh-Oberhuber (M/O) criteria.

Results: 221 out of 347 patients (63,6%) had anti-tTG titers ≥10 times ULN; among them 216 patients (97,7%) showed lesion degree of 2, 3a, 3b, 3c according to M/O; 5 patients (2,3%) showed lesions type 0 (1 pt) and 1 (4 pts) according to M/O and were diagnosed as potential CD. 126 out of 347 patients (36,4%) had anti-tTG levels < 10 times ULN. Among them, 93 patients (73,8%) showed lesion degree 2, 3a, 3b, 3c MO; 33 (26,2%) received diagnosis of potential CD (lesions type 0,1 M/O).

Conclusion: Our data suggest that the "biopsy-sparing" protocol is applicable to patients with anti-tTG titer ≥ 10 times ULN and positive EMA, regardless of the presence of typical symptoms, as 4 out 5 of patients considered potential CD had infiltrative lesions at histology (type 1 M/O lesions).

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Objectives and Study: Coeliac disease is characterized by small intestinal inflammation that leads to mucosal damage and malabsorption. Iron deficiency anemia (IDA) is one of the most prominent and sometimes sole manifestation of celiac disease. It has been known that H. pylori, a common cause of peptic ulcer disease is associated with reduced iron stores and iron deficiency anemia as well. The aim of this study was to examine the effect of concurrent H. pylori infection on clinical and laboratory findings in coeliac patients with anemia.

Method: Data of biopsy-proven coeliac disease patients &LT; 18 years of age who had IDA at diagnosis were compiled. A total number of 183 celiac patients with Marsh III histopathological findings in duodenal biopsies were enrolled into the study. Patients were classified into 2 groups according to the presence or absence of H. pylori infection. Laboratory parameters at admission and at the 3rd month of iron supplemented (daily 4 mg/kg) gluten free diet were evaluated.

Results: Iron deficiency anemia was detected in 104 (56.8%) of the patients. The mean age was 7.6 ± 4.7 years and 66% were female. H. pylori infection was confirmed with both rapid urease test and histopathological examination in 33 out of 104 (31.7%) patients. The mean age was higher in H. pylori (+) group. There was no difference between the groups in terms of hemoglobin level and mean corpuscular volume both at admission and at the 3rd month of the treatment. However, ferritin level was significantly lower in H. pylori (+) compared to H. pylori (-) group. Despite of strict gluten free diet supplemented with iron treatment for 3 months, anemia recovered in only 58% of the coeliac patients with IDA. The rate of treatment resistant IDA was higher in H. pylori (+) group compared to those not infected with H. pylori (63% vs 32% respectively, p=0.004).

Conclusion: Iron deficiency anemia is one of the most frequent manifestations in coeliac disease. In anemic coeliac patients, concurrent H. pylori infection might require longer iron replacement. Since iron is mandatory for cognitive and psychomotor development in childhood, iron deficiency anemia in children with coeliac disease would require investigation of H. pylori infection at diagnosis. Furthermore iron status of patients must carefully be considered during the follow-up period.
The impact of the gluten free diet on growth in children with celiac disease: a comparison between Italian and American children

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Objectives and Study: To evaluate the impact of the gluten free diet on anthropometric parameters (weight, height and body mass index z scores) of celiac children diagnosed either in Chicago, USA or Verona, Italy.

Methods: An international collaborative retrospective study was conducted for patients seen at the Universities of Verona and of Chicago. Inclusion criteria: positive serology and Marsh 1–3 findings on biopsy; or TTG IgA >10 times normal with positive EMA in the absence of biopsy. Exclusion criteria: underlying syndromes (Down, Turner, Ehlers-Danlos).

Results: We enrolled 265 celiac children: 140 from Chicago and 125 from Verona. The female: male ratio was 2:1 and the mean age at diagnosis was 7.32 years (SD±3.91) in Verona and 8.4 years (SD±4.7) in Chicago (NS).

At the time of diagnosis, Italian celiac children had a weight slightly but not significantly lower (p=0.06) than their American counterparts, with no difference in height (p=0.7). Of note, the BMI z score was significantly (p=0.0004) higher in the American celiac children. While the majority of patients had normal BMI in both countries, 6% of Italian celiac children vs 17% of US celiac children at time of diagnosis were overweight/obese.

After following a GFD (gluten free diet) for at least one year, there was a significant increase in height (p&LT; .0001 for both groups) and weight (p=0.009 for Italian celiac children and p&LT; 0.0001 for US celiac children) z score. No change was found in BMI z-score (p=.1335 for Italian celiac children and p=.0646 for American ones). Interestingly, while on GFD, Italian celiac children showed an increased prevalence of both, underweight as well as overweight; while their American counterparts on the contrary showed a slight decrease of overweight/obese.

Conclusion: We conclude that at the time of diagnosis, Italian celiac children had a significantly lower BMI than American celiac children. There was an overall similar impact of the GFD on growth of celiac children in both countries; however, the BMI z score rose more in American than in Italian celiac children. Such different impact of the GFD in the two settings is likely attributable to lifestyle differences, such as the larger reliance on naturally gluten-free vs processed gluten-free foods in Italy.

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A double-blind placebo-controlled study of vitamin D supplementation in newly diagnosed children with coeliac disease

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Objectives and Study: Children with coeliac disease (CD) may experience deficiency of several micronutrients at diagnosis. Vitamin D deficiency (< 20 mg/mL) and insufficiency (21-29 mg/mL) is a frequent finding at diagnosis of CD. The objectives of the present study were to assess the effect of a low-dose vitamin D supplementation on vitamin D serum concentration and bone mineral density in a double-blind placebo-controlled 12 months' study.

Method: Newly diagnosed children (< 17 years) with CD were eligible to participate. Excluded were patients with diabetes mellitus, thyroid diseases, and other conditions known to affect bone metabolism. After signing informed consent, each patient was randomized to receive ether 400 IU of vitamin D and 400 mg of calcium per day, or placebo. Treatment was continued for 6 months. Serum concentration of Calcium, Phosphate, 25 hydroxy vitamin D (25OHD) and parathyroid hormones were measured at baseline, and after 2, 6 and 12 months. Lumbar spine and total body bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry at baseline, and after 6 and 12 months.

Results: We enrolled 33 newly diagnosed patients. Three did not complete the study, and were not included in the final analysis. Of the remaining 30 patients, 16 were randomized in the treatment arm and 14 in the placebo group. The two groups did not differ in sex distribution, age, and anthropometric measurements. At baseline, the median 25OHD concentration was 28.9 mg/mL and 23.3 mg/mL in the treatment and placebo groups, respectively. One patient had vitamin D deficiency and 8 vitamin D insufficiency at baseline in the treatment group. After 2 and 6 months of supplementation, the deficiency was corrected, and 5 patients showed insufficiency. At 12 months, the distribution was back to baseline. The number of patients of the placebo group with deficiency were 6 at baseline, 3 at 2 months, none at 6, and 5 at 12 months. Patients with insufficiency were 3 at baseline, 5 at 2 months, 1 at 6 months and 3 at 12 months. Calcium and phosphate concentrations did not change over time in both groups. BMD z-scores improved over time in the two groups, and the difference between the two treatments was not significant.

Conclusion: Our data show that a high proportion of newly diagnosed patients with CD have hypovitaminosis D. A low-dose supplementation with vitamin D improves hypovitaminosis, and its suspension restores the baseline situation. A prolonged supplementation is recommended, particularly in all cases in which vitamin D deficiency is present at diagnosis.

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GASTROENTEROLOGY - Coeliac disease

G-P-059

The prevalence of Helicobacter Pylori in Celiac Cases and its effect on clinic, histopathology and laboratory parameters

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Objectives and Study: In this research we have studied the prevalence of Helicobacter Pylori in children with Celiac Disease (CD) and the relations of HP with clinic, histopathology and laboratory parameters.

Methods: 256 patients who were serologically and histopathologically diagnosed celiac disease at Cukurova University, Medical Faculty, and Pediatric Gastroenterology Department between the dates of January 2012 - March 2016 were taken to the study. Besides obtaining duodenum biopsy through upper GIS endoscopy, antrum biopsy was also taken and histopathological HP existence and histological damage level were studied. The cases detected HP (+) and HP (-) were compared according to their age, gender, applied complaints, clinic and laboratory features.

Results: 70 (27.4%) of 256 cases in the study were detected HP (+). During the period of this study, HP (+) was found in upper gastrointestinal system endoscopy of 270 (26.7%) cases among the 1012 cases with dyspeptic complaints. There was no significant difference between HP (+) and HP (-) cases according to their gender and age. In HP (+) cases while the diagnose age was older, the complaints for diarrhea and abdominal distension were significantly higher. In the histopathologic examination of small intestines of HP (+) patients with celiac disease; 16 (23%) cases were Marsh 3A, 39 (55%) cases were Marsh 3B and 15 (22%) cases Marsh 3C. In HP (-) cases, 61 cases were 3A (33%), 71 cases were 3B (38%), and 53 cases were 3C (28%). In the stomach biopsy of HP (+) cases with CD, activity and chronicity was significantly higher than the HP (-) cases with CD. Atrophy was detected in 2 HP (+) cases and intestinal metaplasia was detected in 3 cases. Iron deficiency anemia in HP (+) and HP (-) cases was detected as respectively 51% and 47%. Although hemoglobin, ferritin, vitamin B12 and transfer saturation were lower in HP (+) cases comparing to HP (-) ones, the differences were not statistically significant. Serum folate level in HP (+) group was significantly low (p< 0.05). Additionally, significant differences were not detected between the groups from the aspect of SD scores of weight and height.

Conclusion: In our study, it was observed that; the prevalence of HP does not increase in cases with celiac disease, CD is lately diagnosed in HP (+) cases, distension and diarrhea complaints are more frequent, and folate deficiency is significantly higher. We think the reason for late diagnosis in HP (+) CD cases is caused by not considering CD since the HP was already diagnosed. We believe that for HP (+) cases, in presence of the distension and diarrhea complaints in advanced childhood period, physicians should consider Celiac disease.

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Evaluation of eye findings in children with Coeliac Disease

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Objectives and Study: To investigate tear parameters and optical coherence tomography (OCT) findings in children with Coeliac Disease

Method: 100 eyes of 50 children followed-up with coeliac disease were included in the study. 110 eyes of 55 healthy children were included in the study as the control group. Basal tear production was calculated by applying the standard Schirmer test under topical anesthesia. Tear break-up time (BUT) were determined using fluorescein. Pupil dilatation was achieved with 1% tropicamide. 9x9 mm macular sections and 6x6 mm optical disc sections were taken with spectral domain OCT (Nidek RS 3000; Nidek Co., Ltd., Aichi, Japan).

Results: The mean Schirmer test was 20.20 ± 3.93 mm in the control group and 14.07 ± 5.14 mm in the patient group and the difference was statistically significant (p &LT; 0.0001). Similarly, the mean BUT was 15.25 ± 2.49 in the control group, 10.86 ± 3.51 in the patient group, and the difference was significant (p &LT; 0.0001). The mean total retinal thickness (TRT) was 252.33 ± 21.66 µ in the patient group and 262.58 ± 17.63 µ in the control group and the difference was statistically significant (p &LT; 0.0001). The outer retinal thickness (ORT) was 214.87 ± 11.84 µ in the control group, 196.69 ± 14.93 µ in the patient group and the difference was significant (p &LT; 0.0001). The mean cup / disc (C / D) ratio was 0.28 ± 0.13 in the control group, 0.41 ± 0.12 in the patient group and the difference was significant (p &LT; 0.0001). Similarly, optic nerve thickness (ONT) was significantly thinner in the patient group compared to the control group (p &LT; 0.0001).

Conclusion: In the present study, TRT, CRT, IRT, ORT and ONT were found to be thinner in the coeliac disease patients than the control group. However, it was also found that there were significant changes in tear parameters.

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**The increased prevalence of celiac disease: what is the contribution of an improved diagnostic accuracy?**

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**Objectives and Study:** In the last years an increase in frequency of coeliac disease (CD) has been observed. We aimed to evaluate the rate of "potentially missed CD cases" by screening studies based on anti-gliadin (AGA) IgA antibodies in order to compare prevalence rates from current studies (based on anti-transglutaminase-TTG IgA or anti-endomisium -EMA antibodies).

**Method:** Stored sera samples collected from HLA DQ2/DQ8 predisposed children with a known status of anti tTG an and EMA ab, already detected in a screening project in Italy were analyzed with AGA IgA ELISA kit (Ridascreen, Eurospital). For each patient 2 EMA and tTG negative, HLA predisposed subjects were tested as matched controls (same sex, age and ethnicity). CD was diagnosed according to the ESPGHAN 2012 criteria. Children with IgA-deficiency were excluded.

**Results:** A total of 138 HLA predisposed children of them 46 samples were anti tTG ab and EMA positive samples (untreated CD) and 92 samples were anti tTG ab and EMA negative samples (controls) were tested for AGA IgA. Out of 46 untreated CD samples 28 (61%) detected positive and 18 (39%) detected negative by AGA IgA immunoassay. Out of 92 Control samples, 4 (4.3%) detected positive and 88 (96.7%) detected negative from AGA IgA ELISA test. The sensitivity, specificity, positive predictive value and negative predictive values of the AGA IgA were found to be 61%, 96%, 87.5% and 83% respectively.

**Conclusion:** Previous prevalence studies based on AGA IgA as the initial screening test would have underestimated the prevalence of CD with a potential rate of missed cases of 39%. This discrepancy should be taken into account when comparing current prevalence of CD (based on EMA as screening technique) to previous figures.

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Objectives and Study: Presence of a specific major histocompatibility complex (or human leukocyte antigen, HLA) DQ2 and/or DQ8 is considered an essential risk-factor for the development of Coeliac Disease (CD). About 90% -95% of patients with CD have HLA DQ2/DQ8 haplotype and HLA DQ2/DQ8 typing is considered as an additional diagnostic test. Conventional PCR-based HLA typing method is expensive, time-consuming and requires well-trained personnel. We aimed to assess the efficacy of Celiac Gene Screen Kit, a new-fangled sequence-specific, primer based rapid single PCR reaction HLA method for detection of HLADQ2/DQ8 alleles.

Method: For the detection of the sensitivity of the Celiac Gene Screen Kit 99 EDTA samples with a known HLA status were selected, where HLA genotyping has already been characterized by SSO-PCR testing. We performed rapid HLA typing using Celiac Gene Screen kit, (BioDiagene S.r.l.) for the identification of samples susceptible to Coeliac Disease performed in one PCR reaction. The kit foresees a rapid DNA extraction (1 min), a DNA amplification and a detection using a fluorescence reader. Presence or absence of HLA-DQ2/ DQ8 alleles was determined in further 431 samples with unknown HLA status (suspected CD n= 157, CD family members n= 72 and healthy controls n=103) using BioDiagene rapid HLA haplotype detection test.

Results: Out of the 99 known status of HLA DQ samples, 79 were reported HLA DQ positive and 20 were reported HLA DQ negative conventional SSO-PCR method. All 79 reported HLA DQ positive and 20 reported HLA DQ negative by Celiac Gene Screen kit well. This showed an excellent concordance rate between testing by a conventional method and rapid method. Among unknown status of HLA DQ samples, 129 (82.1%) of 157 of suspected CD, 48 (66.7%) of 72 CD family members and 52 (50.5%) of 103 controls samples were either/or HLA-DQ2/DQ8 positive by Celiac Gene Screen kit.

Conclusion: Celiac Gene Screen kit method showed an excellent concordance with the SSOP-PCR test. Celiac gene screen could be a cost-reducing and an effective tool for CD gene screening.

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The presentation of Coeliac disease: Urban and Rural regions of Turkey

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Objectives and Study: Coeliac disease (CD) is an autoimmune-inflammatory disorder triggered by the ingestion of gluten-containing grains in susceptible individuals. The development of CD is determined by both environmental and genetic factors. Living in urban or rural regions may potentially alter the clinical presentation. The aim of this study was to determine and compare the clinical pattern of CD in rural versus urban parts of Turkey.

Method: Patients with CD were retrospectively evaluated in this multi-center study. Patients were classified into 2 groups according to geographic region where they lived: The Marmara region, Urban group and the eastern Anatolia and the south-eastern Anatolia region, Rural group. Two groups were compared in terms of demographic data, clinical presentation of the patients and associated disorders.

Results: A total of 594 CD patients (urban group 277, rural group 317) were enrolled. The main age of the children at diagnosis was older in the rural group, compared to the urban group, 9±4 years vs 7.7±4.4 years, respectively (p=0.001). No difference was found between two groups in terms of gender distribution, weight, or height z-scores at presentation. Abdominal pain as the presenting symptom of coeliac disease was higher in the urban than the rural group (48.4% vs 31.4%, p=0.001) whereas constipation was higher in the rural group (23.5% vs 9.4%, p=0.001). The rate of CD-associated conditions, including type 1 diabetes, autoimmune thyroidal disease, IgA deficiency, Down and Turner syndrome did not differ between the groups. Consanguineous marriage (19.8% vs 28.7%) and the presence of a first-degree relative with CD (9% vs 20.7%) were significantly higher in the rural group (p<0.05). The diagnosis rate of asymptomatic CD through family screening was significantly higher in the rural group (1.1% vs 17.7%).

Conclusion: There were differences between the rural and urban regions of Turkey in terms of age at diagnosis of CD, presenting symptom and the rate of diagnosis through family screening. A higher age at diagnosis of CD in the rural regions might be secondary to the difficulties in reaching the second level health care or other environmental factors, which affect the evolvement of the disease. The higher rate of diagnosis of asymptomatic celiac patients through family screening seemed to be related to the higher rate of consanguinity among the parents in this cohort.

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Change in clinical pattern of pediatric coeliac disease

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Objectives and Study: The classic manifestations of coeliac disease (CD) are primarily related to gastrointestinal system. Besides, non-gastrointestinal symptoms such as chronic iron deficiency anemia, short stature, osteoporosis, dermatitis herpetiformis, hypertransaminasemia and neurological symptoms might be the presenting symptoms in non-classical form of coeliac disease. The clinical presentation of coeliac disease has changed in recent years, and non-gastrointestinal symptoms outweigh malabsorptive manifestations. The aim of this study was to evaluate the changing clinical pattern of CD in Turkey.

Method: Hospital database of the CD patients was retrospectively analyzed for this multi-center study. Patients were divided into 2 groups according to the time of diagnosis: Group 1 before 2010 (diagnosed between January 2000-December 2010) Group 2 after 2010 (diagnosed between January 2010-December 2017). Children who had the diagnosis of CD before and after 2010 were compared by taking the demographic data, clinical presentation at diagnosis, associated disorders and histopathologic findings into consideration.

Results: Group 1 and 2 consisted of 139 (7.1±4.1 years, 58.3 % female), 460 (8.8±4.2 years, 60.5 % female) coeliac patients, respectively. No difference was found between two groups in terms of gender distribution, weight, or height z-scores. The main age of the children at diagnosis was older in group 2, compared to group 1 (p=0.001). After 2010, the most common clinical presenting symptoms were constipation and short stature whereas abdominal pain and diarrhea were more common in coeliac patients who had the diagnosis before 2010. The rate of diagnosis of asymptomatic coeliac patients through family screening (presence of index case in the same family) was significantly higher in group 2, compared to group 1 (10.7% vs 3.6%, respectively) (p=0.03). The epidemiological and presenting features of patients were shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=139)</th>
<th>Group 2 (n=460)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>49.6%</td>
<td>36.1%</td>
<td>0.005</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38.1%</td>
<td>27.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.3%</td>
<td>20.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Short stature</td>
<td>0.7%</td>
<td>9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>57.6%</td>
<td>56.9%</td>
<td>0.92</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>16.5%</td>
<td>21.7%</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>4.3%</td>
<td>8.2%</td>
<td>0.14</td>
</tr>
<tr>
<td>Consanguineous marriage</td>
<td>8.6%</td>
<td>17.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Family history of CD</td>
<td>2.9%</td>
<td>12.2%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusion: Over the past 20 years, there has been a change in incidence, age at diagnosis and the presenting symptoms of celiac disease all over the world. The average age of coeliac patients at diagnosis increased significantly. The diagnosis of asymptomatic coeliac patients through family screening increased in this cohort. This may be due to increased awareness of not only the high
prevalence of coeliac disease but also the higher incidence of CD in family members among physicians. Furthermore, the proportion of children presenting with classical malabsorptive symptoms decreased while atypical or extra gastrointestinal symptoms such as constipation and short stature has increased in this cohort.

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Clinical and serological characteristics of children with ultra-short coeliac disease

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Objectives and Study: In approximately 10% of children with coeliac disease the histological findings are limited to the duodenal bulb (ultra-short coeliac disease). It is not clear, however, whether this group of children has different clinical parameters or outcome from children with coeliac involving the second part of the duodenum. The aim of our study was to identify clinical and serological characteristics at baseline and at follow up of children with ultra-short coeliac disease.

Methods: We included children with coeliac disease from the paediatric gastroenterology unit, "Dana-Dwek" children’s hospital, from October 2009 to November 2017. All children had positive anti-tissue transglutaminase (TTG) antibodies and histological findings consistent with coeliac disease. Two biopsies were taken from the duodenal bulb and four from the second part of the duodenum in all children. We compared clinical and serological data of children with an isolated duodenal bulb involvement to children with involvement of the second part.

Results: A total of 648 patients were included in the study: 393 (60.6%) females and 225 (39.4%) males. Seventy-one children (11%) had an isolated duodenal bulb involvement with median (IQR) age of 7.5 (5.7-10.1) years compared to 6.4 (3.9-10), p=0.005. In the former group, the prevalence of diarrhea at diagnosis was lower (2.8% versus 16.1%, p&LT; 0.01) and they presented less anemia (7% versus 20.5%, p&LT; 0.01) and lower anti-TTG levels at diagnosis (10% versus 58.2% with anti-TTG antibodies exceeding 10 times the upper limit of normal, p&LT; 0.01). At follow up under gluten free diet, this group presented a non-significant trend of shorter time to normalization of anti-TTG levels with median (IQR) of 3 (3-6) compared to 5 (3-9.75) months, p=0.088. There were no differences in family history of coeliac disease, body mass index, duration of symptoms before diagnosis or gastric involvement between the groups.

Conclusion: The prevalence of ultra-short coeliac disease in children was 11%. This group of children presented with unique characteristics: less diarrhea and anemia and lower anti-TTG levels at diagnosis, with a trend of shorter time to normalization of anti-TTG under gluten-free diet.

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Classifying pediatric acute pancreatitis into mild, moderately severe and severe!

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Objectives and Study: NASPGHAN Pancreas Committee recently classified pediatric pancreatitis as mild, moderately severe and severe depending upon the presence or absence of organ failure and local complications. The aim of this study was to study the relative incidence of these three types among children with acute pancreatitis, to describe the difference in clinical features and lab parameters in these three classes and to assess the role of various biochemical markers like Serum Amylase, Lipase, Albumin, CRP, Total Leucocyte Count and hematocrit to predict the severity (moderately severe or severe) of the disease.

Method: Records of the children admitted to a single institution with acute pancreatitis from 2010 to 2017 were reviewed. They were classified into three groups- mild, moderately severe and severe after reviewing the history and clinical course summary from the hospital information system. Demographics, duration of hospital stay, etiology and laboratory parameters such as serum amylase, lipase, total leucocyte count, hematocrit and CRP at the time of admission were recorded. Chi², unpaired t-test, ANOVA, Pearson Correlaton coefficient and ROC were used for statistical analysis.

Results: Records of 134 children with acute pancreatitis were reviewed. 16(11.9%) were less than 5 years, 46 (34.3%) were 5-10 years, 54 (40.3%) were10-15 years and 18(13.4%) were 15-20 years of age. 77 (57.5%), 44 (32.8%) and 13 (9.7%) had mild, moderately severe and severe disease respectively. In the three groups, Mean hospital stay was 5.71±2 days, 11.82±6.2 days & 15.08±7 days. Mean Amylase level was 844, 514 and 691 IU/L. Mean lipase level was 1041, 445 and 575 IU/l. Mean TLC was 11879, 15175 and 16384/mcl. Mean Albumin was 3.77, 3.31 and 2.90 gm/dl and Mean CRP was 42, 134 and 152 respectively.

There was clinically significant difference in the duration of hospital stay (p=.000), Serum Lipase level(p=.003), TLC (p=.018), CRP (p=.000) and Albumin(p=.000) among the three groups and there was no significant difference in age, amylase and hematocrit levels in the three groups.

There was moderately strong positive correlation between CRP and length of hospital stay (r=0.5, p=0.00) and moderately inverse correlation between S. Albumin level and length of the hospital stay(r=-0.4,p=0.00). There was weak positive correlation between Total leucocyte count and Hospital stay (r=0.23, p=0.00).

Receiver operating curve analysis showed that Serum albumin levels were better for predicting moderately severe and severe cases of acute pancreatitis than CRP or WBC levels on day 1 (area under the curve [AUC], 0.8 versus 0.79 and 0.63, respectively)

Conclusions: There were significant differences in the lab parameters among the mild, moderately severe and severe pancreatitis groups. Prognostic factors like Serum Albumin, CRP and Total Leucocyte Count were found to be useful in predicting on the development of the severe form and the length of the hospital stay.

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A first approach for an evidence-based method to adjust PERT in pediatric patients with Cystic Fibrosis

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Objectives and Study: The aim of this project was to assess the effectiveness of a method to adjust pancreatic enzyme replacement therapy (PERT) in Cystic Fibrosis (CF) based on the prediction of the optimal dose according to food properties, by means of modelling of results of in vitro digestion studies.

Method: A prospective interventional study was carried out including 43 patients from 5 European centres. During 24h they followed a fixed diet (5 meals), along with the theoretical optimal dose of enzymes for each meal previously predicted by in vitro digestion studies and derived models. Fat in stools was determined in a central lab after samples collection, which was carried out using colorimetric markers for a precise identification of stools corresponding to the study meals. For statistical analysis, beta regression models were applied to explain the relationship of study variables with coefficient of fat absorption (CFA).

Results: Median CFA was 90% (95% CI 84, 96%) with no differences among centres. Patients’ compliance with protocol was 99% and median Bristol stool scale was 3-4. No association of CFA with age, mutation or BMI z-score, but a significant effect was found with transit time (p&LT; 0.05). Our findings suggest that these variables do not play as an important role as food characteristics do on lipids digestion (on the basis of which the study doses were established).

Conclusion: Applying the in vitro predicted PERT dose for each meal, the clinical target of CFA is reached with low variability among patients. The proposed approach can be considered a first step towards an evidence-based method to adjust PERT in CF.

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Characterizing patterns of fecal elastase-1 in a paediatric nutrition and gastroenterology center (gastronutriped) in colombia

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Objectives and Study: Exocrine pancreatic insufficiency (EPI) is a frequent and underdiagnosed entity in paediatrics. Fecal elastase 1 (FE-1) is an easy and reliable test for the diagnosis of EPI in patients with or without CF. The objective of this study was to describe the characterizing pattern of FE-1 in children in a paediatric nutrition and gastroenterology center (Gastronutriped) in Bogota, Colombia.

Method: Descriptive retrospective approach that included patients between 3 months and 15 years of age whose FE-1 levels were determined in a sole fecal sample by means of the use of a commercial ELISA (Schebo-Tech, Giessen, Germany) in a period between January, 2012 and April, 2015. Its normal concentration is established by the manufacturer as 200 µg/g. The levels of FE-1 were classified as >200 µg/g (normal exocrine pancreatic function); 100-200 µg/g (slight to moderate EPI) and < 100 µg/g (severe EPI). The data were analyzed by using Stata 13. For the categorical variables, absolute and relative frequencies were used, and for the continuous ones measures of central tendency and dispersion. The chi-square test was used (significance < p = 0.05 with one tail) in order to determine the association of FE-1 with premature birth and with the use of pancreatic enzymes.

Results: 51 patients were included, with a median age of 20 months. 13.7% had abnormal results for FE-1. The patients with chronic diarrhea and malabsorption had values in the range of moderate EPI, and all of the patients with values in the range of severe EPI presented with a diagnosis of cystic fibrosis (CF). 25.39% had a history of premature birth, with significant differences of EPI between the children with a history of prematurity Vs full-term newborns (p 0.577). 11.76% of the patients were undergoing enzyme replacement therapy (ERT) on testing for FE-1, and 83.3% of the patients with ERT continued to have altered FE-1 (p 0.000). (Table 1)

<table>
<thead>
<tr>
<th>Level FE-1</th>
<th>Normal</th>
<th>EPI Slight-moderate</th>
<th>EPI severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>12 (92.3%)</td>
<td>1 (7.7%)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Full term</td>
<td>32 (84.2%)</td>
<td>3 (7.9%)</td>
<td>3 (7.9%)</td>
<td>38</td>
</tr>
<tr>
<td>Use of enzyme replacement during the test for FE-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (16.7%)</td>
<td>2 (33.3%)</td>
<td>3 (50%)</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>43 (95.5%)</td>
<td>2 (4.5%)</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

Conclusion: FE-1 is useful and non-invasive for the diagnosis of EPI of different etiologies. Normalization of FE-1 was not found in patients with ERT. The routine implementation in the study of malabsorption in paediatrics would be of great help. More studies are required in order to determine if there is a difference in the values of FE-1 in children of different ages and gestational age. Table 1. Distribution of the pancreatic function for patients according to the levels of FE-1, gestational age, and use of enzyme replacement therapy, in a paediatric nutrition and gastroenterology center (Gastronutriped) 2012-2015.

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Chronic pancreatitis in children: may anatomic defects and gene mutations coexist in the same patient?

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Objectives and Study: Chronic pancreatitis in children is mainly caused by genetic mutations. Obstructive and anatomical causes, mostly represented by pancreas divisum, are the second cause. Children with chronic pancreatitis and anatomical defects may also have genetic mutations, often on multiple genes.

Methods: We report the case of an adolescent girl with chronic pancreatitis and both genetic and anatomical causes.

Results: A 12-year-old Pakistani girl was admitted to the Emergency Department for acute abdominal pain. Her past medical history was characterised by recurrent abdominal pain with vomiting usually at spontaneous resolution. An increase in lipase (>3 ULN), aminotransferases (ALT >2 ULN) and serum GGT (3 ULN) was recorded at blood exams. Abdominal ultrasound showed diffuse pancreatic parenchymal damage. CT scan revealed dilatation of Wirsung and Santorini ducts with a normal biliary tree. The magnetic resonance cholangiopancreatography (MRCP) confirmed the dilatation of Wirsung and Santorini ducts showing multiple ductal stones and anatomical defects compatible with pancreas divisum. The pancreas was rather atrophic with diffuse inflammation and peripancreatic fluid. During endoscopic retrograde cholangiopancreatography (ERCP) sphincterotomy of minor and major duodenal papilla was performed with placement of two stents leading to a progressive clinical and laboratory improvement. At a follow-up visit, about five months later and after stents' removal, the patient was in good clinical conditions without further episodes of abdominal pain. Considering her past medical history, genetic analysis was carried out that revealed a R254W homozygous mutation in CTRC (Chymotrypsin C) gene and a N34S heterozygous mutation in SPINK1 gene. N34S heterozygous mutation in SPINK1 gene is reported both in general population and in patients with pancreatitis. R254W homozygous mutation in CTRC gene occurs in children with chronic pancreatitis even if at a lower incidence than other mutations (PRSS1 43%, SPINK1 19%, CFTR 14%, CTRC 3%).

Conclusion: Our report underlies the importance of investigating chronic pancreatitis-associated genes in every child with chronic pancreatitis even in the presence of anatomical defects such as pancreas divisum.

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The evolution of acute pancreatitis into acute recurrent pancreatitis in children - the impact of etiological factors

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Objectives and Study: The incidence of acute pancreatitis (AP), acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in the pediatric population is rising and becomes a common clinical problem in gastroenterology. Assessment of morbidity risk factors is necessary to improve the quality of diagnostics, to determine further treatment and to identify groups with poor prognosis of the evolution of AP in the ARP and CP.

Methods: In the present study we collected the etiological factors identified in patients with AP and ARP, admitted to Department of Paediatrics, Gastroenterology and Nutrition, Medical University of Wroclaw, between January 2015 to November 2017.

Results: The study group consisted of 38 patients (27 patients with AP and 11 patients with ARP). The potential etiological factor was established in 85.2% of children with AP and in 100% of children with ARP. Mutations in the SPINK1 gene were found in 44.4% of children with ARP, no mutations in the PRSS1 gene were found. In all children with a genetic predisposition (SPINK1 mutation) during the first episode of the ARP, coexistence of an additional predisposing factor, mainly infectious, was found. At the same time, the infectious agent was the most frequent identified cause of ARP (36.3%). In 27.3% of children, the occurrence of ARP was associated with pathology of the bile ducts and pancreas. Medications were responsible for the occurrence of 9.1% of episodes in the course of the ARP, however, in the group of children with a single episode of the AP, the drugs as valproic acid and azathioprine were responsible for 22.2% of symptoms. Abdominal trauma in these group was found as a cause of 11.1% of AP cases, the most common factor was an infection, established in 40.7% of patients.

Conclusions: Patients with ARP require diagnostics towards mutations predisposing to the transition into a chronic disease, however the interaction of additional triggers plays a role in the development of pancreatitis inflammatory disease in genetically predisposed individuals.

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Objectives and Study: Pancreatic cyst is a pathological fluid collection located in the pancreas or directly adjacent to it. Pancreatic pseudocyst is the most common complication of acute or chronic pancreatitis. However, due to the rare occurrence of these entities in children, the knowledge about evolution and management of pancreatic cysts in paediatric patients is still very low. The aim of our study was to evaluate the management of pancreatic cysts in paediatric population.

Method: Clinical data of 57 children with pancreatic cyst treated in a 10-year period (2007-2017) were reviewed comprehensively: 13 with posttraumatic pancreatic pseudocyst, 13 with pancreatic cyst in the course of acute pancreatitis (AP) of other than traumatic etiology, 22 with pseudocysts as a complication of chronic pancreatitis (CP) and 9 patients with cysts of different etiology. The relationship between the etiological factor, treatment method and clinical outcome of the patients was analyzed.

Results: Among 26 paediatric patients with pancreatic cysts in the course of AP, both posttraumatic or not, 5 children (19.2%) were managed by conservative methods (antibiotics, nutritional therapy). Ten children (38.5%) underwent endoscopic treatment. Pseudocysts resolved after endoscopic cystogastrostomy or endoscopic retrograde cholangiopancreatography (ERCP) in 7 children (70%). There were no ERCP-related complications. Seventeen patients (65.4%) were treated by surgical drainage or resection. In 3 patients serious complications occurred, requiring relaparotomy or blood transfusion. Fifteen children (88.2%) after surgery operation had clinical and radiologic resolution of their cysts. Since 2007, 22 of 215 children (10.7%) with CP were diagnosed with pancreatic pseudocyst. Twelve patients (52.2%) were treated by observation. Ten children (45.5%) underwent endoscopic cystogastrostomy or pancreatic duct stenting. Eight children after endoscopic treatment had clinical and radiologic resolution of their PP. Five patients (22.7%) were treated surgically. PP resolved after operation in all cases. There were no complications or failures related to surgical procedures. Some patients fell into more than one category.

Conclusion:
1. Endoscopic or surgical drainage of pancreatic cysts in children is a safe and effective procedure.
2. Asymptomatic cysts can be managed by a period of observation.

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GASTROENTEROLOGY - Cystic fibrosis and pancreatic disorders

G-P-073

Fecal calprotectin in Cystic fibrosis patients during respiratory exacerbation

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Study: CFTR (Cystic fibrosis trans-membrane conductance regulator) dysfunction of the gastrointestinal (GI) tract occurs early in life and is present in all patients with CF (Cystic fibrosis), regardless of genotype. The same pathophysiologic triad of obstruction, infection, and inflammation that causes disease in the airways also causes disease in the intestines - CF Enteropathy. Mucus accumulation in the intestinal lumen in CF creates a niche for abnormal microbial colonization, which can lead to microbial dysbiosis. Significant elevation of fecal calprotectin is noted in many CF patients, suggesting intestinal inflammation. Systemic antibiotic treatment has been shown to improve various systemic inflammatory markers as well as serum and sputum calprotectin. Antibiotic treatment aimed at pulmonary complaints may improve inflammatory GI tract status.

Objective: The aim of the study was to evaluate CF patients' gastrointestinal inflammatory burden, through fecal calprotectin during a pulmonary exacerbation and its change after systemic antibiotic treatment.

Methods: In this Prospective study fecal calprotectin levels were measured at the beginning and the end (day 10 through 14) of systemic antibiotic treatment. Associations between inflammatory markers, clinical and nutritional indices were evaluated in the study group.

Results: The study included 11 patients (mean age [standard deviation (SD)], 28.09[9.7] years, 11 pancreatic insufficient. There was a significant decline in the fecal calprotectin levels from the beginning of the study 223.73µg/g[226.21µg/g] compared to the levels at the end of antibiotic treatment 109.55µg/g [132.68µg/g]; p=0.045. Similarly there has been a significant improvement in FEV1.0 before the start of antibiotics 52.2% [20.92] compared to FEV1.0 at the end of treatment 60.33% [24.25]; p=0.045. There was no correlation between fecal calprotectin, FEV1.0 change and nutritional indices.

Conclusions: Systemic antibiotic may reduce inflammatory burden in the gastrointestinal tract in CF patients during respiratory exacerbation, possibly through change in intestinal microbiome.

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Coexistence of CFTR and SPINK1 mutations in a patient with chronic pancreatitis

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Objectives and Study: Hereditary chronic pancreatitis is rare in pediatric population. CFTR, PRSS1, PRSS2, and SPINK1 mutations have been gene alterations identified to play role in pathophysiology of the chronic pancreatitis thus reducing the percentage of cases previously described as idiopathic. Objectives of the study: to present the first patient in Macedonia with hereditary pancreatitis with coexistence of homozygous mutation of SPINK1 gene and heterozygous CFTR mutation

Method: History, clinical findings, ultrasound examinations, MRCP and mutation analysis.

We present a case of 11 years old girl with 7 episodes of pancreatitis over last 2 years, each of them with nausea, pain in epigastrium, elevated pancreatic enzymes without endocrine and exocrine insufficiency. Hypercalcemia, autoimmune pancreatitis and structural malformations (magnetic retrograde cholangiopancreatography) were excluded. Molecular studies identified coexistence of pathogenic mutation c.3154>G (phe1052Val) of CFTR gene in heterozygous form and analysis of SPINK1 gene identified risk factor variant c.101A>G (p.Asn34Ser) in homozygous form. Changes in these two genes explained the patient’s phenotype. Because of sensorineural hearing loss analysis of GJB2 gene identified pathogenic mutation c.35delG (p.Gly12Valfs) in homozygous form. Subsequently CFTR mutation in heterozygous form was identified in younger sibling who was asymptomatic.

Conclusion: This is the first patient in Macedonia with hereditary pancreatitis with coexistence of homozygous mutation of SPINK1 gene and heterozygous CFTR mutation. Homozygous mutation in SPINK1 gene is never found in asymptomatic subjects. Detection of these mutations can help to establish correct diagnosis and prognosis, and to start early treatment to avoid serious complications in family members.

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Transient elastography is superior to APRI score in detection of cystic fibrosis related liver disease

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Objectives and Study: Transient elastography and APRI score, the aspartate aminotransferase to platelet ratio index, are two diagnostic modalities which can be used in the diagnosis of cystic fibrosis-related liver disease (CFRLD). The aim of this study was to evaluate the usefulness of these modalities in this respect.

Method: An observational study of pediatric cystic fibrosis patients was performed. Each patient had at least one liver stiffness measurement by transient elastography and AST and platelet count determined between January 1st 2009 and April 30th 2016. Diagnosis of CFRLD was made based on Colombo criteria. Measurements of patients with CFRLD were compared to measurements of patients without CFRLD.

Results: A total of 320 measurements of 172 individual patients were eligible for evaluation. 72 measurements were performed in patients with CFRLD. The median liver stiffness was 10.3 (IQR 7.5-20.5) kPa, the median APRI score was 0.46 (IQR 0.30-0.62). 248 measurements were performed in patients without CFRLD. The median liver stiffness was 4.6 (IQR 3.9-5.6) kPa (P< 0.001), the median APRI score was 0.25 (IQR 0.18-0.33) (P< 0.001). Analysis of receiver operating characteristics for detecting CFRLD resulted in cut-off points at 6.3 kPa for transient elastography and 0.31 for APRI score. Transient elastography was superior to APRI score in detecting CFRLD with areas under the curve of 0.94 for transient elastography versus 0.79 for APRI score (P< 0.001) (Figure 1).
Conclusion: Transient elastography and APRI score both seem to be useful modalities in the diagnosis of CFRLD. However these data show that transient elastography is superior to APRI score in this respect.

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Estimation of ultrasound attenuation in diagnostics of pancreatic steatosis in children

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Objectives and Study: The aim of the work was to improve the diagnosis of pancreatic steatosis, which was achieved by determining the coefficient of ultrasound attenuation.

Method: We examined 80 children aged 7 to 17, of which 50 (62.5%) patients had obesity, and 30 (37.5%) patients were not obese. The pancreatic steatosis was evaluated by ultrasonography. In order to diagnose pancreatic steatosis, steatometry of the pancreas was performed - a quantitative estimation of the ultrasound attenuation with determination of average ultrasound attenuation coefficient (aUAC) of the pancreas, performed on UltimaPAExpert apparatus (“Radmir”, Ukraine). We made research with obtaining repetitive values of the ultrasound attenuation coefficient (UAC), 5 measurements were performed in each part of the pancreas with the definition of the mean value.

Results: In group 1, the mean value of the UAC was (2.4 ± 0.39) dB / sm, in group 2 - (1.75 ± 0.29) dB / sm (p < 0.05). The obtained coefficients of ultrasound attenuation were compared with the data obtained in the study of the pancreas during the sonographic research. The ROC analysis of the average coefficient of ultrasound attenuation was conducted to determine the boundary value. According to the ROC analysis, exceeding of the average ultrasound attenuation coefficient of 2.27 dB / sm indicates a presence of steatosis of the pancreas (AUC=0.897, sensitivity 95.7%, specificity 75.0%, p<0.05).

Conclusion: The obtained data show that steatometry (estimation of the coefficient of ultrasound attenuation) is a method that allows to diagnose steatosis in children.

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A ten-year retrospective review of the nutritional management of paediatric patients with pancreatitis at a single tertiary centre

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Objectives and Study: There is a growing body of evidence that prompt nutritional management can improve outcomes in pancreatitis in children, promoting not only recovery but also growth and development. However, there is limited research evidence on the ideal nutritional approach in children and nutrition practices vary. The purpose of this review was to explore the nutritional management of children with pancreatitis at a single tertiary centre.

Method: Medical records of children with confirmed pancreatitis treated in our centre between January 2007 and December 2017 were reviewed. Patients with at least one documented episode of pancreatitis requiring hospitalisation were included. Clinical, laboratory and nutritional data were reviewed. BMI Z-scores were used to categorise overweight (>1.0) and underweight (< 2.0) children according to WHO criteria.

Results: Forty-one patients (25 female) had at least one admission with pancreatitis, with 32% (13) having two episodes and 20% (8) three or more episodes. Patients were diagnosed with acute pancreatitis 56% (23) and chronic pancreatitis 44% (18) and causes included: idiopathic (18), hereditary (8), autoimmune (4), ductal anomalies (3) and other (6). Median (IQR) age at first episode was 11.1 (7.25-13.66) years. Median (IQR) length of stay for the first recorded admission was 5 (3-10) days and nutrition was commenced on median (IQR) day one (1-4). As shown in Table 1, 20% (8) were started on parenteral nutrition (PN), 7% (3) on naso-jejunal feeding (NJF), 27% (11) on a low fat diet and 46% (19) on an unrestricted oral diet. The indications for initiating PN included presence of pseudocyst, pancreatic collection, pain/vomiting. PN was given for a median (IQR) of 8 (4-9) days with only one patient who was commenced on PN on admission requiring it on discharge. PN was stopped in the remaining patients due to line access (3) and enteral tolerance (4). The indication for initiating NJF was pain/vomiting with two patients still requiring NJF on discharge. The indication for initiating a low fat diet was pain/vomiting or consultant preference and all but one patient remained on a low fat diet on discharge. The majority of children were started on an unrestricted oral diet and remained on the same diet on discharge.
<table>
<thead>
<tr>
<th>Type of diet</th>
<th>Indication given for diet choice (N)</th>
<th>Parenteral Nutrition (N)</th>
<th>Naso-jejunal feeding (N)</th>
<th>Low fat diet (N)</th>
<th>Unrestricted oral diet (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral nutrition 20% (8)</td>
<td>Pseudocyst (3), collection (2), pain/vomiting on eating (3)</td>
<td>Pseudocyst (1)</td>
<td>Pain/vomiting (2)</td>
<td>Consultant preference (3) Pain/vomiting on unrestricted diet (1)</td>
<td>Tolerating diet (1)</td>
</tr>
<tr>
<td>Naso-jejunal feeding 7% (3)</td>
<td>Pain/vomiting on eating (3)</td>
<td>N/A</td>
<td>Pain/vomiting (2)</td>
<td>Consultant preference (1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Low fat diet 27% (11)</td>
<td>Pain/vomiting on eating (2), Consultant preference (9)</td>
<td>Pain/vomiting (1)</td>
<td>N/A</td>
<td>Consultant preference (10)</td>
<td>N/A</td>
</tr>
<tr>
<td>Unrestricted oral diet 46% (19)</td>
<td>Tolerating (19)</td>
<td>N/A</td>
<td>N/A</td>
<td>Consultant preference (4)</td>
<td>Tolerating diet (15)</td>
</tr>
<tr>
<td>Total</td>
<td>100% (41)</td>
<td>5% (2)</td>
<td>10% (4)</td>
<td>46% (19)</td>
<td>39% (16)</td>
</tr>
</tbody>
</table>

[Table 1: Diet provided on initiation and discharge]

Median (IQR) vitamin D on presentation was 44.8nmol/L (31.5-61.9). Median (IQR) serum amylase on presentation was 175IU/L (90-389) and was not statistically significantly associated with the type of diet initiated or length of stay. Of those patients with complete growth data (34), mean (SD) BMI Z-score was 0.06 (1.5) at first episode with 6% (2) underweight and 32% (11) overweight/obese. Over a median (IQR) follow-up of 1.29 (0.5-2.8) years, 79% (27) improved or maintained their BMI Z-score.

**Conclusion:** This review has demonstrated that the nutritional status of the majority of children with pancreatitis was improved or maintained irrespective of length of hospital stay or frequency of episodes. Most children were able to commence nutrition on day one of admission, the majority on an oral diet. There were a range of indications given for dietary approach and this may point to the need for clear guidelines on the nutritional management of pancreatitis in children.

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Experience with 1811 Endoscopic Pancreatic Function Tests (ePFTs) in two pediatric gastroenterology centers

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Objectives and Study: Endoscopic pancreatic function test (ePFT) has evolved since the early nineties to serve as a more practical way to assess pancreatic acinar cell function in children. A recently published ESPGHAN/NASPGHAN position paper reviewed the stimulated and indirect exocrine pancreatic function tests and noted a lack of uniformity in performing PFT. Our centers have performed 1811 secretin ePFTs since 2001 in the age group from 0 till 25 years of age. Our goal is to present our technical and clinical experience with ePFT and its value as addition to the regular upper gastrointestinal endoscopy.

Methods: The main indications of the tests were failure to thrive, weight loss, diarrhea, abdominal pain and bloating. Prior to endoscopic intubation 0.2mcg/kg of synthetic human secretin (maximum 16mcg) and/or 0.02mcg/kg of cholecystokinin is given as an intravenous bolus, which resulted in increased pancreatic secretion within 3-4 minutes. After positioning the endoscope at the level of the Ampulla of Vater an aspiration catheter is inserted through the suction channel and 4 aliquots of fluid is aspirated between 3 and 10 minutes after administration. The collected fluid was immediately frozen and pH, protein, amylase, lipase, trypsin, chymotrypsin and elastase activities were measured in our laboratories.

Results: Specimens with pH below 5 and protein less than 0.5mg/dL were discarded as inappropriate specimens. After secretin administration the pH value of the 4 consecutive samples increased by in average between 0.3-0.7 in all age groups. The protein content also increased in the 2nd and 3rd specimens and decreased in the 4th reflecting a dilutional effect. Overall 61% of children had normal pancreatic function test. Selective amylase deficiency was one of the most frequent finding (7.7%) mainly in younger children (<2 years of age). The other large group was children with generalized enzyme deficiency (7.75%). Trypsin deficiency was present in 4.4%. The prevalence of isolated elastase deficiency was 1.7% with otherwise normal enzyme activities. Many of the children had repeat tests and it allowed us recognizing the phenomenon of maturational delay in the pancreatic enzyme secretion.

Conclusions: The advantage of ePFT is the direct collection of the pancreatic fluid during endoscopy in children. Its use in our practice resulted in increased endoscopic diagnostic yield and helped properly manage the symptoms of these children. ePFT allows measurement of not only the enzyme secretion but also to assess the pancreatic duct function. In addition, the collected fluid can be used for other diagnostic purposes (cytokines, protein analysis, etc). The ePFT also can be performed as a combined procedure with endoscopic ultrasound. The main limitation of the ePFT is that it requires general anesthesia in children.

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GASTROENTEROLOGY - Cystic fibrosis and pancreatic disorders

G-P-079

Nutritional status impact on cystic fibrosis liver disease

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Objectives and Study: Cystic fibrosis associated liver disease (CFLD) is the second non-pulmonary cause of death in cystic fibrosis, which, beside pulmonary disease, became one of the most important management issue. Lung function is influenced by the nutritional status, therefore the effect of the nutritional grade on CFLD would be important to be assessed. The aim of this study is to evaluate the effect of the nutritional status on the cystic fibrosis associated liver disease - CFLD outcome.

Method: Study included sixty-three patients with cystic fibrosis prospectively monitored for ten years. They were routinely followed-up by clinical assessment, liver biochemical tests, ultrasound examinations and elastography. CFLD was diagnosed using ECFS criteria. All patients with CFLD received ursodeoxycholic acid 20 mg/kilo body weight. Body mass index was used to evaluate the nutritional status expressed by percentages and z-scores.

Result: More than two third of patients (74.6%) were diagnosed with CFLD and weight deficit, without significant gender gap. About 7% of patients leave the study. Under-weighted children associated various vitamins deficiency and the reduced BMI was a significant risk factor for the development of CF severe liver disease (pLT; 0.01). Severe CFLD, with portal hypertension was frequent in thin children, in a 81.06% of patients.

Conclusion: Low BMI is frequently associated with CFLD. To what extent one feature is influenced by other remains to be established. An adequate nutritional intervention could improve the CFLD outcome.

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Objective and Study: Exocrine pancreatic insufficiency can be a manifestation of a serious problem in children, which may influence their growth and development. Pancreatic insufficiency in children is usually associated with diseases such as Cystic Fibrosis, Shwachman-Diamond Syndrome or chronic pancreatitis, as is the case of idiopathic fibrosing pancreatitis. Several indirect tests are used to confirm pancreatic insufficiency. Fecal pancreatic elastase-1 is a reliable laboratory test for the diagnosis or exclusion of exocrine pancreatic insufficiency. Unlike most pancreatic enzymes it is stable during intestinal passage and is not degraded. It is found to be stable in feces for several weeks when stored frozen, hence the convenience for batch determinations.

Transient pancreatic insufficiency has been rarely described and data on this entity is lacking in the medical literature. We found only one case report that described severe pancreatic insufficiency after gastrointestinal infection with enterovirus.

In this retrospective study we aim to report 27 cases of transient pancreatic insufficiency presented with failure to thrive and/or diarrhea and low transient fecal elastase-1.

Method: We followed 43 children (age range 1 months - 18 years) with low fecal elastase-1 in our institution between the years 2009-2017. We followed their growth charts and laboratory results (particularly, CBC, albumin, transaminases, celiac serology, sweat test and fat soluble vitamins). Elastase levels below 200 were considered as pancreatic insufficiency.

Results: We identified 43 cases with low stool elastase in our database. Sixteen were excluded due to missing data or being syndromatic. Enrolled children were all otherwise healthy. The median age at diagnosis was 5.3 years (range 0.1-15 years), 13 females and 14 males .Their main presenting symptoms were failure to thrive and/or diarrhea. Median elastase levels were 93.6 (range 0.67-180). Median time for normalization was 11.8 months (range 2-36 months). Abdominal sonography, celiac serology and sweat test were normal for all patients. Most patients were treated with pancreatic enzymes until resolution.

Conclusion: Transient exocrine pancreatic insufficiency without clear etiology should be in the differential diagnosis of exocrine pancreatic insufficiency after ruling out known etiologies. The resolving course pattern may be attributed to an unidentified infectious agent. Further studies to assess the etiology are mandated.

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Body composition measured by BIA of tube-fed cystic fibrosis (CF) patients compared to age-sex matched CF controls

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Objectives and Study: Body mass index has been recognized as an important indicator of clinical condition in CF. However, recent studies indicate that lean body mass (LBM) is an even stronger indicator. In the nutritional treatment of CF, tube feeding (TF) is often used to improve the nutritional status. The influence of TF on body composition is not yet evaluated, which was the aim of this study.

Method: BIA measurements were performed in CF patients with (TF) (2F, 7M) and without TF (Co). Fat%, body fat mass index (BFMI) and fat free mass index (FFMI) were calculated. Indices were used to account for height differences. Patients were matched for age, gender and pancreatic function. Results are given as median (quartiles).

Results: At the start of TF patients were 12.8 (8.7;15.6) yrs old, had a Height (H) z-score of -2.7 (-2.8; -1.7) and a BMI z-score of -2.1 (-2.9; -1.4). The median time they were on TF before the BIA measurement was 1.5 yrs (0.84; 2.7). There was a significant improvement in BMI z-score (p= 0.038) and H z score (p=0.008).The age at BIA measurement was 14.4 (12.5;16.5). TF patients were significantly shorter than Co (p=0.001) but the BMI z-score as well as pulmonary function (FEV1%, FVC%) were not significantly different between TF and Co. The body composition, however, was significantly different with a higher Fat% (p=0.024) (TF: 24.7 (19.6;33.1) and Co: 12.9 (10.8;22.1)) a higher BFMI (p= 0.019) (TF: 4 (3.3;5.7); Co: 2.5 (1.95;3.85)) and a lower FFMI (p= 0.04) ( TF: 11.8 (10.9;13.4); Co 15.1 (13.2;17.25) in TF patients. There was no relation of body composition with age at start TF, duration of TF or pulmonary function. The BMI z-score at start TF was positively correlated with Fat% (p=0.032) and BFMI (p=0.01).

<table>
<thead>
<tr>
<th></th>
<th>Start TF (12.8 (8.7;15.6) yrs)</th>
<th>BIA measurement (14.4 (13.3;16.5) yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H z-score</td>
<td>BMI z-score</td>
</tr>
<tr>
<td>TF-Group (2F/7M)</td>
<td>-2.7 (-2.8; -1.7)</td>
<td>-2.1 (-2.9; -1.4)</td>
</tr>
<tr>
<td>Co-group (2F/7M)</td>
<td>-0.1 (-0.85; 0.2)</td>
<td>-0.4 (-0.9; -0.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.22</td>
</tr>
</tbody>
</table>

[Clinical data]

Conclusion: Patients receiving TF have less LBM. Although tube feeding is often the only remaining way to restore nutritional status in CF patients, it leads to increased body fat proportions. Different TF types as well as interventions combining activity to TF should be evaluated in the future.

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Variation in Faecal elastase-1 reference levels in different regions of the world: an analysis and result from Indonesian children

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Objectives and Study: Faecal elastase-1 (FE-1) is the most trusted indirect test to evaluate the exocrine pancreatic function in children. It is noninvasive, convenient, and has high sensitivity and specificity in diagnosing severe exocrine pancreatic insufficiency. Reference levels for certain laboratory parameters can be different in Asian populations, such as hemoglobin and vitamin D. A number of literatures showed that the mean level of FE-1 tends to be higher in Asian population. Studies from Asian populations such as China (966.9 µg/g) and Japan (1504 µg/g) showed lower mean FE-1 level in general than studies from other populations such as the United States (403 µg/g), Brazil (500 µg/g), Norway (534 µg/g), England (437 µg/g), Turkey (279 µg/g), and Serbia (648 µg/g). Another joint study from Russia, England, Poland, and Greece also revealed lower mean FE-1 level (636.7 µg/g) than the Asian populations. Based on this fact, there is a need to confirm this difference by taking sample for FE-1 level in Indonesia as a representative of another Asian population, Indonesia. The aim of this study is to obtain the cut-off level of FE-1 in Indonesian children.

Methods: This is a cross-sectional study in 120 healthy asymptomatic Indonesian children, 6-60 months of age, with no gastrointestinal symptoms, taken through random sampling from several kindergartens in Jakarta. Subjects were assessed by medical doctors to exclude any possible illnesses, including malnutrition. One-time stool sample was taken and FE-1 level determined using ELISA method (ScheBo® kit), which use two monoclonal antibodies specific for elastase-1 in human pancreas. In this study, the median and percentiles level was used to determine the cut-off point due to abnormal distribution of data. The cut-off point will be determined from the level of FE-1 at 5th percentile (P5) or 10th percentile (P10), based on which level is closer to the globally accepted cut-off level (200 µg/g) and clinical judgment.

Results: The mean level of FE-1 in healthy Indonesian children is 1304 µg/g (±786 µg/g), while as a comparison, control assay remains in normal range. The distribution of FE-1 level was classified into 3 different age group categories: 6-23 months, 24-60 months, and 6-60 months. Level of FE-1 in each age group category were similar to each other. Therefore, the 10th percentile of FE-1 level in 6-60 months category was taken as the cut-off point (307 µg/g). The determination of cut-off point at P10 is based on the consideration that, firstly, the level at P10 is closer to the cut-off point used globally, and secondly, because FE-1 mean level observed in Indonesian children tends to be higher than the other countries.

Conclusion: The mean and cut-off level of FE-1 in Indonesian children as a representative of Asian countries is consistently higher than other populations. Further studies might be needed to determine the difference in FE-1 among populations and factors contributing to it.

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Objectives and Study: D-lactates are produced by the intestinal biota and later absorbed into the circulation. Some patients with cystic fibrosis develop exocrine pancreatic insufficiency that may disturb gut microbiome and enhance D-lactates production. However, this issue has not been studied yet. The aim of the study was to assess the concentration of D-lactates in relation to the occurrence and activity of gastroenterological disorders in patients with cystic fibrosis.

Method: Serum concentrations of D-lactates were measured in 38 patients with cystic fibrosis, aged from 6 months to 18 years (the average age of 7.8 years), 19 girls and 19 boys. The analysis included age, sex, clinical symptoms, diet (the variety and calorie needs) and the laboratory tests for the exocrine- and endocrine pancreatic efficiency, faecal calprotectin the marker of intestinal inflammation, parameters of liver damage and of cholestasis.

Results: The average activity of cystic fibrosis in Schwachmann-Kulczycki score was 74.2. The clinical presentation of cystic fibrosis was determined by the symptoms of exocrine pancreatic insufficiency (in 76.3%), recurrent respiratory infections (in 60.5%) and undernutrition (in 47%). The median level of D-lactates was 0.86 µg/ml (1-3Q:0.48-2.03) and correlated with the CF activity in the Schwachmann-Kulczycki score, parameters of exocrine pancreatic insufficiency and the presence of inflammation.

Conclusion: Serum D-lactates concentration is a new promising marker of intestinal flora dysbiosis/overgrowth related to exocrine pancreatic insufficiency in patients with cystic fibrosis.

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Mucinous cystadenoma of the pancreas in a 14-month-old Thai girl: a case report

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Objectives and Study: Mucinous cystadenoma of the pancreas is a rare tumor in children; very few patients were reported in literature. It is a benign but premalignant lesion with approximately two thirds occurring in the body or tail of the pancreas.

Method: We report a case of pancreatic mucinous cystadenoma in a 14-month-old girl with a huge pancreatic cyst.

Results: She presented with abdominal discomfort and swelling with elevated serum lipase. Abdominal ultrasonography and CT scan showed a large well-defined rim enhancing cystic mass about 14 cm. with mass effect to surrounding structure and unidentified pancreas. Cysto-gastrostomy and cyst wall biopsy were done initially. After histological diagnosis of mucinous cystadenoma of pancreas, she underwent another laparoscopy and complete removal of tumor.

Conclusion: Pancreatic cystic neoplasms especially mucinous cystadenoma are very rare in children and should be included in differential diagnosis of pancreatic cyst. Complete surgical removal is mandatory to prevent turning into malignancy.

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GASTROENTEROLOGY - Cystic fibrosis and pancreatic disorders

G-P-085

Phenotypic and genotypic characteristics of infantile exocrine pancreatic insufficiency

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Objectives and Study: Exocrine pancreatic insufficiency is a rare disease. We performed whole exome sequencing in children with this disorder.

Method: We enrolled 3 patients with exocrine pancreatic insufficiency. Patients were characterized on phenotypes and radiologic findings. Whole exome sequencing was performed. This study was approved by the Ethical Committee of Children's Hospital, Fudan University.

Results: In all, three children were identified. Average age of disease onset was two months. Patients presented with chronic steatorrhea and failure to thrive. Imaging showed pancreatic lipomatosis and metaphyseal dysplasia. For these patients with similar phenotypes, whole exome sequencing revealed two patients had novel UBR1 mutations (c.3040_3044delAAAG/c.3848+6T>C and c.4290T>G/c.1850-2A>T), and another patient had homozygous SBDS c.258+2T>C mutation. All patients received pancreatic enzyme replacement therapy. Follow-up showed catch-up growth among patients.

Conclusion: We here described two patients with Johanson-Blizzard syndrome and one patient with Shwachman-Diamond syndrome. Whole exome sequencing should be applied for definite diagnosis.
[Fig. 1 Abdominal CT showed pancreatic lipomatosis in patient with Johanson-Blizzard syndrome.]

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Deep enteroscopy with a through-the-scope balloon catheter system in pediatric patients with IBD

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Objectives and Study: Early and accurate diagnosis and extension of inflammatory bowel disease (IBD) is important for correct therapeutic decisions, prognosis, and follow-up. The NaviAid™AB device (Smart Medical Systems Ltd.) is an on-demand through-the-scope balloon system for small bowel evaluation which can be utilized for both anterograde and retrograde approaches. We evaluated the NaviAid™AB contribution in diagnosing and assessing the extent of the disease in the small bowel of children with IBD.

Method: Prospective, open, single-center study includes children aged 8-18 years with known or suspected IBD, which underwent enteroscopy utilizing the NaviAid™AB (anterograde, retrograde or both). The balloon catheter is inserted through the instrument channel of a standard endoscope and advanced ahead of the endoscope. The balloon is then inflated to an anchoring pressure with repetitive push-pull technique to easily advance the endoscope deep into the small bowel. Procedural times, depth of insertion, ease of use, findings, and adverse events were recorded.

Results: 31 patients (14.6; range 9-18 years; 51.6% male) referred for 48 endoscopic procedures were prospectively enrolled. Known IBD (45.2%) or suspected IBD (54.8%). Out of 48 procedures, 9 were excluded from the study (8 during retrograde procedure), due to stricture of the ileocecal valve (3), inadequate bowel preparation (2) and/or technical difficulties (4). 17 procedures were designated for anterograde approach and 22 for retrograde approach (total of 39). The median depth for NaviAid™AB insertion was 80 cm (range 40-110 cm) from the papilla in the anterograde approach and 65 cm (range 30-90 cm) from the ileocecal valve in the retrograde approach. The average advancement time utilizing the balloon catheter was similar between the two approaches (anterograde 7:46 min. retrograde 7:02 min.). 76.3% of all procedures were reported as easy, no procedures were reported above moderate. Among 5 patients with undetermined colitis the NaviAid™AB confirmed the diagnosis of UC in 4 and Crohn’s Disease (CD) in 1 patient. NaviAid™AB provided data of disease extent in the examined small bowel in all patients (known or suspected CD). In contrast to the retrograde examination, no pathology was found in the anterograde examinations. There were no procedural adverse events reported.

Conclusion: The NaviAid™AB device, by using a conventional colonoscope, contributes safely and effectively to the accurate diagnosis and extension of IBD in children. The through-the-scope catheter allows deep and easy advancement into the small bowel in shorter time and may prevent the need for additional endoscopic procedures or imaging in the near future.

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The spectrum and outcome of upper gastro-intestinal bleeding in children from two tertiary centres in Eastern India

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Objectives and Study: Gastrointestinal bleeding is not uncommon in children. Upper GI bleeding is less common than lower GI bleed. A prospective study has been carried out to find out the aetiology and management outcome of upper GI bleeding from a tertiary centre in Eastern India.

Method: This prospective study was conducted at 2 tertiary GI centres in Kolkata from May 2011 to May 2017. Children aged 1 month to 16 years presenting with Hematemesis, altered blood in vomitus or Malena either in outpatient or in emergency were studied to find out

- The aetiology of Upper GI bleed
- Incidence and causes according to age group
- Outcome of management

Children with Upper GI bleeding whose parents did not agree to do endoscopy were excluded from the study. All children were investigated with Upper GI Endoscopy. Meckel's scan, MR/CT Enterography and CT angiography were done whenever Upper GI Endoscopy failed to find any cause.

Results: A total of 167 children were included in this study for whom aetiological investigations were completed. Among them 91(54.5%) were male. All the children were distributed according to age group and the distribution was as follows: 29(17.4%) were Infants, 51 (30.5%) were between 1 - 6 years, 62(37.1%) were between 6 -12 years and 25 (15%) were above 12 years. The predominant cause of GI bleeding was gastroduodenal ulcer and erosions (68%) followed by variceal bleeding(12%). 2 infants with Hematemesis had Hyperplastic antral polyp - one had laparoscopic polypectomy and another had Endoscopic removal with endoloop insertion. Argon Plasma Coagulation was done in all children with Angioectasia and Dieulafoy's lesion. All Duodenal ulcers(Forest 1 and 2) were treated with thermocoagulation(silverprobe) and hemoclip was applied in one. Adrenaline injection was done in few erosions with active bleeding. All Oesophageal varices were treated with Endoscopic Variceal Band Ligation(EVL). Ulcers which were not bleeding actively were left alone and were treated with injectable Esomeprazole during hospitalization and later switched to oral Esomeprazole before discharge. One 4 year old girl was diagnosed to have Menetrier's disease secondary to Cytomegalovirus infection and she improved on conservative management. All erosion and ulcers in infants were due to Cow's Milk Protein Induced Gastroenteropathy.15 children had Duodenal ulcers and H pylori was positive in 20 children with gastro-duodenal ulcers. On follow up for 1 year no children had any recurrence of bleeding.
### Aetiology of bleeding in different ages

<table>
<thead>
<tr>
<th>Causes</th>
<th>Infants (n=29)</th>
<th>Above 1 year upto 6 years (n=51)</th>
<th>above 6 years upto 12 years (n=62)</th>
<th>above 12 years upto 16 years (n=51)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions &amp; Ulcers</td>
<td>20</td>
<td>35</td>
<td>43</td>
<td>14</td>
<td>112 (67%)</td>
</tr>
<tr>
<td>Varices</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>13</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>12 (7.2%)</td>
</tr>
<tr>
<td>Mallory Weiss Tear</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td>Vascular lesions (Angioectasia and Dieulafoy’s lesion)</td>
<td>2 (angioectasia)</td>
<td>1 (Dieulafoy’s)</td>
<td>1 (Dieulafoy’s)</td>
<td></td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Antral Hyperplastic Polyp</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td>Menetrier´s Disease</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Nasal Ulcer</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4 (2.4%)</td>
</tr>
</tbody>
</table>

**Conclusion:** This study comprised largest number of children presenting with GI bleeding among all the Indian series. It revealed a different aetiology (ulcer and erosion) of upper GI bleeding like that of western data which is different from all Indian studies where variceal bleed predominated as aetiology. This proved that variceal bleeding is not the predominant cause of GI bleeding in all parts of India and cannot be generalized for this diverse population. GI bleed can be managed effectively with all present diagnostic and therapeutic modalities.

Abbreviation: GI - GastroIntestinal

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Response of children with gastric variceal bleeding to n-Butyl-2 Cyanoacrylate (Histoacryl®) glue injection

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Objectives and Study: Treatment of gastric varices is challenging in adult and children. It was shown that n-Butyl-2 Cyanoacrylate (Histoacryl®) glue injection is effective and safe to control bleeding from gastric varices in adult. However, there is few data about its use in children.

Methods: In this retrospective study, the medical records of children with significant upper gastrointestinal bleeding and found to have gastric varices or varices other than oesophageal varices between 2007 and 2017 at Prince Sultan Military Medical city were reviewed. The clinical information, the endoscopic finding, the recurrence of bleeding, occurrence of complications and the mortality within 30 days were reviewed.

Results: We identified five patients who fulfill the inclusion criteria for the study. Four (80%) were boys. The age range from 3 to 15 years. Two (40%) have biliary atresia. Three (60%) have unknown familial liver disease with negative genetic studies. The weight of patients were (8-39) kg. The follow up varied from 2 months to 10 years. Four (80%) had gastric varices at the time of bleeding and one had big duodenal varices. All were injected successfully with n-Butyl-2 Cyanoacrylate (Histoacryl®). The author had special training with adult patients. The bleeding was controlled in all patient. There was no recurrence of bleeding in all patients. Two (40%) underwent liver transplant, one (20%) died in the transplant list two months after endoscopy without recurrence of bleeding and two (40%) awaiting liver transplant. Follow up endoscopy was performed for three (60%) which showed absence of signs that predict bleeding. One patient (20%) had radiological evidence of the glue in chest X-ray. However, he did not have hypoxia and the glue disappeared in six months follow up. None experienced other complication from the treatment.

Conclusion: n-Butyl-2 Cyanoacrylate (Histoacryl®) glue injection is safe and effective in controlling and preventing recurrence of upper gastrointestinal bleeding due to gastric varices and other non-oesophageal varices. Due to limited number of children, multicenter study with more children will show better regarding safety and efficacy of this treatment. The procedure needs special training before practicing in children.

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Successful intralesional steroid injection treatment in the management of resistant esophageal strictures

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Objectives and Study: Refractory esophageal strictures pose a difficult challenge to both patient and the physician and usually require repeated attempts at dilatation. Post corrosive and post esophageal atresia anastomotic strictures are the most frequent types of esophageal strictures seen in children. Intralesional triamcinolone injections are among various techniques used for the management. Studies support the usefulness of intralesional steroid in refractory strictures. We aim to report our experience of intralesional triamcinolone injections combined with endoscopic dilatations in refractory esophageal strictures.

Method: Retrospective charts review of 6 children who had refractory post corrosive and post esophageal anastomotic esophageal strictures, who underwent endoscopic and intralesional triamcinolone injections were done.

Results: Intralesional triamcinolone injection was performed in six patients, mean age of 3 years and five of them were males. Two patients with caustic-induced esophageal strictures and four patients with anastomotic esophageal strictures. The strictures were 2-6 cm in length. Triamcinolone acetonide (40 mg/mL) was used with the maximum dose of 40 mg. The dilatation index time decreased from 1.11 (1.43-0.64) to 0.58 (1.0-0.4) after triamcinolone injection. The mean number of dilations required was 20 over a mean of 18.8 months before steroid injections and two dilatations over a mean of 12 months after steroid injections. There was improvement in the esophageal inner diameter from 1-4 mm to 6-7 mm before and after steroid injection respectively, as well as dramatical improvement in dysphagia symptoms. Five of six were able to swallow solid foods. No complications were reported after the steroid injections.

Conclusion: Intralesional steroid injections in children with refractory esophageal strictures is safe and beneficial. Further prospective case controlled study is required.

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Investigation of the use of midazolam and ketamine in sedation in pediatric endoscopy

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Objectives and Study: The aim of this study is to investigate the efficacy and safety of the sedation induced by the intravenous midazolam and ketamine during the upper endoscopy in children.

Method: This study was conducted on patients between the ages of 3 to 18 years, who underwent upper endoscopy. All subjects received IV midazolam and ketamine. During the intervention, hypoxia, tachycardia, bradycardia, hypertension and hypotension; after the intervention euphoria, dysphoria, vertigo, visual problems like diplopia and nystagmus the older children can express himself was questioned and emergencies like arrhythmia, convulsion, hallucination and other findings were recorded.

Results: The mean age of the study group was 11.9±3.42 years and 54% of the patients were females, 46% were males. Regarding the complications emerged during the upper endoscopy, hypoxia was encountered in 9% of patients, mild hypertension in 14%, hypotension in 5%, tachycardia in 23%, bradycardia in 8% and flushing-urticaria in 2% of patients. The incidence of the sore throat, which was one of the most common complications encountered after the upper endoscopy, was 24%. The incidence of vomiting was 14%, dizziness 24%, diplopia 27%, euphoria 3% (5 patients), dysphoria 4%, hallucination 4%. 4% of patients required oxygen supply with a face mask.

Conclusion: The results of our study show that IV midazolam and ketamine was safe and effective in the upper endoscopy of children.

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Clinical and endoscopic findings of caustic ingestion in children at a third level hospital in Mexico

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Objectives and Study: Describe the clinical and endoscopic findings of caustic ingestion in children who received care at the Instituto Nacional de Pediatría (INP) in Mexico City between June 1, 2006 to June 30 2016.

Method: Retrospective, descriptive, transversal, observational study. We describe sixty-eight children who ingested caustic substances and received care at INP between June 1, 2006 to June 30 2016. Descriptive statistics were used.

Results: Of the 68 patients, 45 were male (66%). Median age was 24 months. The most common gastrointestinal manifestation was sialorrhea, which was found in 36 patients; 15 patients had oral ulcers; 10 had non-induced emesis; 7 had dysphagia; 3 had retrosternal chest pain; and 3 had hematemesis. All patients underwent upper endoscopy. 70% of patients showed Maratka 0-I lesions. Of whom, 11 were asymptomatic, 25 showed one clinical manifestation, 10 showed two clinical manifestations, and 2 showed three clinical manifestations. 20 patents showed Maratka grade II and III lesions clinically. Of whom, 2 were asymptomatic, and 18 showed gastrointestinal symptomatology, with the most common being sialorrhea (13 patients), followed by oral ulcers (7 patients) (figure 1). Of the latter 18 patients, 8 showed one clinical manifestations. All patients were kept nil per os (nothing by mouth). Most patients received antimicrobial therapy and corticosteroids (33/48.5%); 21 patients (30.9%) received antimicrobial therapy, corticosteroids and omeprazole; 10 patients (14.7%) received antimicrobial therapy, corticosteroids and ranitidine; and the rest of the patients (4) received monotherapy with either an antibiotic or ranitidine. 13 patients (19.1%) had complications; of whom, 1 (1.5%) had an early complication, 9 (13.2%) had late complications, and 3 (4.4%) had both complications (early and late).

Conclusion: Caustic ingestion in children is an important public health issue. As opposed to the medical literature, we did not find an association between endoscopic findings and clinical manifestations, therefore, we consider clinical manifestations to be poor predictors for the presence and extension of oesophageal and gastric lesions. Thus, endoscopy is the best method for the diagnosis of caustic ingestion in children.

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Objectives and Study: Acute gastrointestinal graft versus host disease (GVHD) is one of the most frequent, serious and feared complications after autologous haematopoietic progenitor cell transplantation in children, with a reported incidence up to 90% (according to the HLA disparity) and a mortality of 50%. The GI tract is often involved and biopsies taken through endoscopy is the preferred diagnostic method. The objectives were to describe the most frequent endoscopic findings in patients with acute GI GVHD and to determine in which site it is more likely to find histopathologic changes to diagnose acute GI GVHD.

Method: We reviewed clinical records of patients with acute GI GVHD that underwent endoscopic procedures during January 2010 to August 2016. Age, gender, underlying disease, post-transplant days at the time of endoscopy and endoscopic findings in the esophagus, stomach, duodenum, rectum, sigmoid and the rest of the colon were described. Also, the GI site where most biopsies where positive to acute GI GVHD according to recent consensus (gland apoptosis) was identified.

Results: Clinical records of 25 patients diagnosed with acute GI GVHD were reviewed. The mean age of presentation was 118 months with a predominance of male sex, the most common underlying diagnosis was acute lymphoblastic leukemia, followed by non-malignant haematologic diseases and primary immunodeficiencies. The mean time when endoscopic study was performed was 72 days. Of the 25 patients, 20 went both upper and lower GI endoscopy and 5 went only upper GI endoscopy (due to adverse effects secondary to bowel preparation). The most frequent endoscopic findings were stomach and sigmoid with erythematous mucosa, and normal appearance mucosa on esophagus, duodenum and non-sigmoid colon. One patient had ulcers on sigmoid. 11 patients had duodenal biopsies taken with no complications reported. All of the 20 sigmoid biopsies (100%) taken where positive to acute GI GVHD.

Conclusion: Upper and lower gastrointestinal endoscopy is still the diagnostic method of choice for acute GI GVHD and it is safe to perform in children. The most frequent findings are mucosal erythema in stomach and sigmoid, the latter being the site with the greatest diagnostic sensitivity. Therefore, in patients who cannot undergo bowel preparation, sigmoidoscopy with biopsy is enough to diagnose acute GI GVHD.

Abbreviations: GI: gastrointestinal
GVHD: graft versus host disease

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Objectives and Study: Experience of hypnosis in gastrointestinal endoscopy is scarce, especially in children. Our aim was to assess the efficacy, tolerance and predictive factors of success of hypnosis used for gastrointestinal endoscopy in children.

Method: This prospective single center study included children aged more than 6 years, requiring a gastroscopy or rectosigmoidoscopy for a diagnosis purpose, and whose parents gave informed consent. Exclusion criteria was deafness, mental retardation or psychiatric problems and a foreign langage. Hypnosis was performed according to Ericksonian method by trained endoscopy nurses. Success of hypnosis was defined a priori as ability to complete the entire endoscopic procedure (including biopsies) associated to good tolerance assessed by the patient at the end of the examination using a specifically designed questionnaire. Levels of satisfaction of the endoscopist, nurse and patient were assessed after the procedure by standardized questionnaire. Associated sedation procedures were registered.

Results: 140 children (70 boys, median age 12 years: 9.0;14) were included between June 2016 and July 2017. They underwent a gastroscopy in 50.7% (n=71), rectosigmoidoscopy in 48.6% (n=68), both in 0.7% (n=1). Associated conscious sedation used equimolar mixture of oxygen and nitrous oxide in 64 patients (46%) associated with oral midazolam in 71 cases (51%). Physical restraint was required in 18 patients (13.4%). Procedure was interrupted and switched to general anesthesia for poor tolerance in 11 patients (7.8%). Success rate of hypnosis reached 82.9%. Predictive factors for success were older age (13 years versus 8 years, OR: 1.34, IC 95% [1.10- 1.62], p=0.003) and type of endoscopy (failure was 16-fold more frequent in case of gastroscopy compared to rectosigmoidoscopy). Level of satisfaction was high for all the evaluators (endoscopist: 84.8%, nurse: 86%, child: 92.1%) and was associated to success of hypnosis.

Conclusion: Hypnosis associated with equimolar mixture of oxygen and nitrous oxide and/or midazolam offers an efficient and well tolerated method to perform diagnostic gastrointestinal endoscopy in children without systematic need of contention nor general anesthesia.

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Objectives: Chronic pancreatitis is defined as a continuous inflammatory pancreatic disease, characterized by irreversible morphological changes, often associates with pain and sometimes with the loss of endocrine and exocrine function. Recurrent pancreatitis (RP) is a challenging condition, it can progress to chronic pancreatitis. Endoscopic ultrasonography (EUS) may detect early stages of tissue change that occurs as a result of fibrosis in pancreatic parenchyma. The aim of this study was to evaluate the information gathered by EUS, in order to diagnose and evaluate recurrent/chronic pancreatitis in children.

Materials and methods: We evaluated the pediatric patients with chronic and recurrent pancreatitis between September 2007 and September 2017, retrospectively. There were 17 patients (10 female, mean age 13.4 years) with chronic/recurrent pancreatitis, through clinical information (according to INSPIRE Group Criteria), magnetic resonance cholangiopancreatography (MRCP) and EUS. Demographic findings, number of attacks, EUS and MRCP results were evaluated.

Results: Seventeen patients admitted for EUS assessment. Follow-up time was 39.8 months in average (range: 9-89 months). Each patient had minimum 3 attacks and maximum 15 attacks. The reasons underlying recurrent/chronic pancreatitis were familial progressive intrahepatic cholestasis (PFIC) type I, cystic fibrosis, APECED syndrome, glutaric acidemia and familial hyperlipidemia in each, the other 12 patients' etiologies were unknown. The laboratory results showed that mean amylase level was 1997.5 ± 366 IU/L (range: 180-10181), lipase level was 1173 ± 108 IU/L (range: 140-4000). The initial evaluation included transabdominal ultrasound (US) and MRCP, then the patients underwent to EUS. There were only two patients who had normal EUS findings. One of them also normal on MRCP and US. The most common finding of EUS was hyperechoic strands in pancreas parenchyma which was found of 15 (%88) patients. The other frequent findings were hyperechoic duct wall (n=5, 29.4%), lobularity (n=4, 23.5%), dilatation of the main pancreatic duct (n=4, 23.5%) and nonshadowing hyperechoic foci (n=2, 11.8%). Even though there were three patients with normal MRCP, they were showed hyperechoic strands and lobularity on EUS.

Conclusions: EUS provides high-resolution imaging of the pancreas determining detailed parenchymal and ductal assessment. Although there is no enough experience in pediatric population yet, it seems to be accurate modality to evaluate the pancreas in children with recurrent/chronic pancreatitis.
[Cysts (1), dilatation of the main pancreatic duct (5.2mm), hyperechoic duct wall (2) lobularity (3).]

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Wireless capsule endoscopy is a useful tool for evaluating the small bowel involvement in IBD paediatric patients

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Objectives and Study: Conventional endoscopy presents limitations for inflammatory bowel disease (IBD) diagnosis in children. Wireless capsule endoscopy (CE) allows exploring the entire small bowel (SB). The objective is to provide our experience with CE in paediatric patients with IBD.

Method: Pillcam Wireless capsule® was administered by mouth or placed by endoscopy. After eight hours registry, images were discharged on the workstation and analysed.

Results: A total number of 55 CE studies were performed in 47 patients with suspected IBD (4-15 years); in 2 extra cases CE was not carried out because the Patency pill showed stenosis. In 11 cases IBD diagnosis was discarded with de CE study. In those 36 cases with confirmed IBD:
- in 7 patients Crohn's disease (CD) diagnosis was achieved due to the CE examination; in 2 cases ileoscopy was not achieved, 2 more had MRI without pathological findings, in 2 cases MRI was not performed due to age or other issues plus ileoscopy was not achieved, and in the remaining case TC scan was normal and colonoscopy and histology unspecific; in this case colonoscopy and ileoscopy performed several years later confirmed CD.
- In 7 cases with colonic disease and with no definitive histological results CE was performed but no SB findings were obtained. In one out of these 7 perianal fistulae appeared and thus CD diagnosis was finally established.
- In 21 additional cases, CE was performed to evaluate CD extension in order to obtain an accurate classification. It was noteworthy the presence of aphthae or ulcers affecting different segments of the upper SB tract in almost all cases and this while the MRI was normal in those areas. Eight patients underwent CE to asses mucosal remission or relapse. Unfortunately in 3 cases out of 21 CE was retained in the stomach during the whole registry period and thus the CE exploration was not valid; in the 3 patients CE evacuation was achieved without incidents. The last case refers to a girl who had complicated perianal fistulae without any other symptoms. Upper endoscopy, colonoscopy, histology, MRI and also CE showed no findings. A colonoscopy performed some years later established CD diagnosis.

Conclusion:
- CE is a suitable technique for exploring the SB.
- CE allows discarding IBD.
- It is striking the presence of characteristic lesions throughout the digestive tract, even in proximal areas, in all our patients with CD.
- CE is well tolerated in children older than 4 years.
CE is extremely useful in selected cases for diagnostic purposes as well as for extension studies and follow up, even in small patients

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Double-balloon enteroscopy experience in children from Turkey

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Objectives and Study: Double-balloon enteroscopy (DBE) was started to use recent years in our country that was allowed detailed, minimally invasive endoscopic evaluation of small bowel mucosa from duodenum to cecum. Although the diagnostic and therapeutic advantages of DBE in adults are well documented, there was limited data in pediatric age group. The aim of this study to investigate the indications, clinical usefulness, feasibility and safety of DBE technic for the diagnosis and treatment of small bowel diseases in children.

Method: The medical files, computer images and videos of the pediatric patients who underwent DBE at our center between 2009 and 2016 were examined retrospectively.

Results: Twenty-four procedure of 15 children (5 girl, 10 male) were included to the study. Mean age of the subjects was 14.02 years (Range: 7-18 years). DBE procedures were performed for abdominal pain (n=5), Peutz-Jeghers Syndrome (n=4), unexplained gastrointestinal bleeding (n=2), chronic diarrhea (n=2), Blue Rubber Bleb Nevus Syndrome (n=1) and Carsinoid Syndrome (n=1). DBE procedures were performed via the oral approach in 10 children, the anal approach in two and both approaches in three children.

Mean length was 199.4 cm with DBE was attained oral approach and also 55 cm with anal approach. Mean procedure duration was 72.6 minutes for oral approach and 55 minutes for anal approach. All DBE procedures were performed in endoscopy unit and under the sedation anesthesia. Polypectomy was performed on five patients for 58 polyp (size from 3 mm to 7 cm). Successful clearance of large polyps by DBE was achieved in all patients. Argon plasma coagulation procedure was performed on 10 hemangiomatosis lesions and band ligation was performed on one hemangiomatosis lesion in Blue Rubber Bleb Nevus Syndrome. Hemorrhage was observed after the three polipectomy procedures (5.1%). Both hemoclips, sclerotherapy, argon plasma coagulation procedures were used. Blood transfusion was not required in any patients. We did not observe other complications.

Conclusion: DBE is safe and useful technique for diagnosis and treatment of small bowel disease in pediatric age group.
Predictors for higher pain score after gastrointestinal endoscopies in children

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Objectives and Study: Gastrointestinal (GI) endoscopic procedures are standard of care for the diagnosis and treatment of several GI conditions. These procedures may be associated with discomfort, pain and anxiety, especially in paediatric population. Predictors for complicated recovery after endoscopies, however, are not known. The aim of our study was to identify risk factors for complicated recovery after GI endoscopic procedures in children.

Method: We included children that were electively admitted for GI endoscopies at the pediatric gastroenterology unit, "Dana-Dwek" Children’s Hospital during 2016. We collected demographic, clinical and endoscopic data. Numerical rating scale (NRS) and Faces, Legs, Activity, Cry, and Consolability (FLACC) scales were used for pain scoring.

Results: A total of 284 children were included: 117 (41.2%) males and 167 (58.8%) females, with a median age (IQR) of 10.7 (6.7-14.8) years. Upper GI endoscopy was performed in 268 (94.3%) and lower GI endoscopy in 84 (29.5%). Therapeutic procedures were performed in 6 (2.4%). Sedation included propofol in all children in addition to gas induction (sevofluran) in 34 (12%) and midazolam in 51 (18.1%). In a multivariate analysis, older age (OR 1.017, P< 0.001), diarrhea (OR 4.85, P=0.003), higher pain score before the procedure (OR 7.93, P=0.001), longer procedure (OR 1.027, P=0.005) and higher number of biopsies (OR 1.304, P=0.001) were associated with higher pain score after the procedure. Children with diagnosis of coeliac disease presented lower pain score after the procedure (OR 0.4, P=0.05). Patients with higher pain score before the procedure had longer recovery time (OR 5.28, P=0.001).

Conclusion: We identified several predictors for higher pain score after GI endoscopies in children. Children with these risk factors should be identified before the procedure in order to be appropriately managed.

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GASTROENTEROLOGY - Endoscopy

G-P-099

SUB-10 minute high quality diagnostic ILEO-Colonoscopy including terminal ileal intubation in children is feasible and safe but compromised by poor bowel preparation

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²The Portland Hospital, London, United Kingdom
³Sheffield Children's Hospital, Sheffield, United Kingdom

Objectives and Study: To critically appraise ileo-colonoscopy (IC) practice in a large tertiary centre, where IC is performed by experienced paediatric colonoscopists: indications of the procedure; bowel preparation efficacy; IC completion rates and timings; diagnostic yield; and complications.

Patients and Methods: All patients (pts) referred to the pediatric gastroenterology clinic of Portland Hospital, between 1st July 2015 and 30th June 2016. Data on age, height and weight, gender, surgical history, indications for colonoscopy, bowel preparation given and bowel cleansing efficacy were collected. The following were calculated: percentage of terminal ileal intubation (TII); time to TII; total duration of each procedure; endoscopic diagnostic yield stratified for indication. The number and the type of complications encountered and the number of pts readmitted within 30 days was also recorded.

Results: A total of 1392 pts were referred, and 181 required an endoscopic evaluation of the lower GI tract. The main indications for IC were: recurrent abdominal pain 38.1%; unexplained chronic diarrhoea 16%; suspected IBD 24.9%; isolated rectal bleeding 13.2%; occult GI bleeding 1.6%; unexplained faltering growth 1.6%; IBD restaging 2.6%; miscellaneous 1.6%. TII rate was 100%. Bowel-cleansing was judged as: Grade 1 (excellent) in 49.2%; Grade 2 (good) in 33.7%; Grade 3 (fair) in 13.3%; and Grade 4 (poor) in 3.9%. Median time to TII was 9.8 minutes. Time to TII was lower in those under 5 years (p=0.005). Mean time to TII was: 8.4 minutes in pts with a grade 1 bowel cleansing score; 10.1 minutes in patient with a grade 2 score; 11 minutes in pts with a grade 3 score; and 21.8 minutes in pts with a grade 4 score. A statistical significant difference in time to TII was recorded between procedures carried out with an excellent and those with good bowel preparation (p=0.052) and between fair and poor bowel preparation (p&LT; 0.001). Median time of total procedure including biopsies, from scope insertion until complete withdrawal, was 14.1 minutes. A statistical significant difference in total procedure length according to age group was found and in particular it was shorter in younger pts (&LT; 5 years) (p&LT; 0.001). The positive diagnostic yield was: 11.6% in pts with abdominal pain; 37.9% in pts with chronic diarrhoea; 51.1% in pts with suspected IBD; 29.2% in pts with isolated rectal bleeding; 33.3% in pts with occult GI bleeding; 0% in pts with faltering growth; and 33% in the miscellaneous group.

Conclusions: Appropriately targeted IC in the management of children with GI symptoms, is a safe, fast and useful investigation. TII rates of 100% are achievable and desirable and can be conducted quickly. Poor bowel preparation impacts negatively on this and IC duration may be faster in younger children. The diagnostic yield in isolated recurrent abdominal pain is low but the importance of a reassuringly negative investigation in the overall management of a child and family must be taken in to account.

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Long-term outcomes of caustic esophageal stricture with endoscopic balloon dilatation in Chinese children

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Objectives and Study: To evaluate the long term outcomes of endoscopic balloon dilatation (EBD) in treating caustic esophageal stricture in children.

Method: We retrospectively reviewed the data of all patients who had a diagnosis of CES and underwent EBD from August 1st, 2005 to December 31st, 2014. The primary outcome in this study was EBD success, which was defined as the maintenance of dysphagia-free status for at least 12 months after last EBD. The secondary outcome was to analyze influencing factors associated with EBD success.

Results: Forty-three patients were included for analysis (29 males; mean age at first dilatation 44 months with range 12-111 months). 26 (60.5%) patients had long segment (>2cm) stricture. A total of 168 EBD procedures were performed. Twenty-six (60.5%) patients were considered EBD success. Seventeen (39.5%) patients failed EBD and required stent placement and/or surgery. Patients in the EBD success group had significantly shorter stricture segments when compared to the EBD failure group (t=2.398, P=0.018, OR=3.206, 95%OR: 1.228-8.371). Seven (4.4%) esophageal perforations occurred in 6 patients after EBD. Stents were placed in 5 patients and gastric tube esophagoplasty was performed in 14 patients.

Conclusion: 26 (60.5%) of 43 children with CES had EBD success. Length of stricture was the main influencing factor associated with EBD treatment outcome.

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Combination of trans-oral and trans-anal double balloon enteroscopy can achieve a high percentage of coverage of the small bowel

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Objectives and Study: The role of double balloon enteroscopy for real time imaging, biopsies and therapeutic interventions in the small bowel is increasingly recognised. Whilst there are studies reviewing the degree of concordance of results between double balloon enteroscopy and wireless capsule endoscopy, there are none to our knowledge reviewing what small bowel coverage can be achieved with double balloon enteroscopy when compared to wireless capsule endoscopy.

Method: We present 10 cases where a double balloon enteroscopy was performed followed immediately by a wireless capsule endoscopy and compare the small bowel coverage between the two modes of endoscopy.

Results: The mean age of this cohort was 9.9 years (range 11 months to 16 years). 50% were male. Commonest indication for double balloon enteroscopy was polyposis (4)(previously identified on conventional endoscopy, wireless capsule endoscopy or previous double balloon enteroscopy), gastrointestinal bleeding (2) and suspected Crohn's (2). The remaining two had a diagnosis of diaphragm disease and suspected intestinal lymphangectasia. In four patients pan-enteroscopy was achieved. In 3 an incomplete wireless capsule study occurred, on 1 of whom a pan-enteroscopy had been acheived. A large proportion of the small bowel was visualised in the remaining patients.

Conclusion: We demonstrate that in the hands of an experienced endoscopist, the majority of the bowel can be reached using the combination of a trans-oral and trans-anal double-balloon endoscopy, allowing for biopsies and real-time interventions to be undertaken.
Gastrointestinal endoscopy and alarm findings in children with chronic abdominal pain

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Study: Clinicians assessing children with chronic abdominal pain (CAP) have the task of (i) discovering causative tissue damage (so called ‘organic pathology’) when present; (ii) making judicious use of investigations; and (iii) convincing patients and their families of the validity of the concept of functional gastrointestinal disorders (FGID), when relevant. Outcome studies of children with CAP indicate that some clinical features are more strongly associated with organic pathology (OP) than others: so called ‘alarm findings’ (AFs). Gastrointestinal endoscopy (GIE) is increasingly undertaken as part of the CAP assessment (1, 2). When endoscopically detectable organic pathology (EDOP) is found in this context, it is reasonably assumed to be the cause of the pain and provides a treatment target.

Objectives: To determine: (i) the diagnostic yield of GIE for all children attending a tertiary gastrointestinal service (King’s College Hospital, London) with CAP as one of their primary symptoms; (ii) the effect on diagnostic yield of making the presence of AFs as a sine qua non for GIE on children with CAP; and (iii) whether a faecal calprotectin in the normal range was a predictor of non-contributory GIE.

Method: A two by two table comparing positive and negative diagnoses with the presence and absence of AFs was constructed. Another two by two table was used to compare AFs and diagnostic outcomes. The relationship between positive faecal calprotectin and OP was determined by crosstabulation. Statistical significance was measured using Chi-square and Fisher’s exact test. Statistical analysis of the data was carried out on SPSS (Chicago) Statistics 22.

Results: 28.4% (23/81) of children for whom GIE was undertaken during the study period were given an organic diagnosis. Just under half (37/81 or 45.7%) did not have AFs and of these, only one had OP (gastro oesophageal reflux disease). Of the 44 patients who had AFs exactly half had OP (P< 0.001)). All 81 subjects had a calprotectin level checked prior to undergoing GIE; 74/81 had a level below the lab cut off value and of these, 20 had EDOP. Of the 7 subjects with a calprotectin level above the lab cut off value, 3 had EDOP. Weight loss (P< 0.001)) and bloody diarrhoea (P=0.01) were the AFs most likely to be associated with OP.

Conclusion: The diagnostic yield of GIE as an investigation for children with CAP attending KCH GI service was low, but in the subgroup who had CAP plus AFs was much higher. Applying AFs strictly as a screening tool in this group of patients would have led to loss of supportive evidence of a diagnosis of gastro oesophageal reflux disease in a single patient.

References:
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<td>Localised abdominal tenderness</td>
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<td>Perianal abnormalities</td>
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<td>Skin changes</td>
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<td>Back pain</td>
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**[Alarm Findings in CAP]**
Diagnostic and therapeutic approach to obscure gastrointestinal bleeding in children: experience of two quaternary referral centers

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Objectives and Study: Even though obscure gastrointestinal bleeding (OGIB) accounts for a small fraction of cases, it continues to pose a diagnostic and therapeutic challenge to gastroenterologists. To date, there are no guidelines regarding the approach to pediatric OGIB. Aim of this multi-centre study is to present our experience as quaternary referral centers on the diagnosis and management of OGIB in children.

Methods: Multi-centric, retrospective study, on patients (pts) aged 0-18 yrs with OGIB, admitted to Sheffield Children’s Hospital of Sheffield (UK) and to Umberto I Hospital of Rome (Italy).

Results: From January 2007 to January 2017, 60 pts with OGIB were admitted. 45 presented with overt gastrointestinal (GI) bleeding (9 melaena, 35 blood per rectum and 1 both melaena and blood per rectum), and 15 with an occult GI bleeding. Ten presented with severe anaemia requiring at least one blood transfusion. Those pts underwent on average 1.6 upper GI endoscopies and 1.8 lower GI endoscopies. Diagnostic approach included Wireless Capsule Endoscopy (WCE) in 46, Double Balloon Enteroscopy (DBE) in 15, Single Balloon Enteroscopy (SBE) in 23, laparoscopy-assisted enteroscopy (LPE) in 3, abdominal MRI/MRE in 20, CT abdomen in 1, CT angiography in 2 and Meckel’s scan in 25. WCE identified a lesion in 31/46 (67.3%), DBE in 13/15 (86.7%), SBE in 19/23 (82.6%), LPE in 2/3 (66.7%), MRI in 7/20 (35%) although with 1 false positive (3.6%). CT angiography was negative in all and CT abdomen identified a lesion in 1 (100%). Meckel’s scan was true positive in 1/25 (4%), truly negative in 15/25 (60%), and false positive in 9/25 (36%). Diagnosis was made in 40: small bowel (SB) angiodysplasia (9), small bowel and retroperitoneal angiomatosis (1), Blue Rubber Bleb Nevus Syndrome (BRBNS) (2), SB Crohn’s disease (4), Cowden syndrome (1), Peutz-Jeghers (5), Meckel’s diverticulum (2), eosinophilic enteritis (3), SB juvenile polyp (5), duodenal ulcer (1), peri-anastomotic ulcers (2), volvulus (1), SB diaphragm disease (1), duplication cyst (1), polyposis syndrome with PTEN mutation (1) and jejunal varices (1). In 19 pts (31.7%), no source of bleeding was found.

20 pts underwent endoscopic therapy (Argon Plasma Coagulation (APC)/ endoclips/ polypectomy). 2 had LPE with endoscopic polypectomy. One received both LPE and surgery for Meckel’s diverticulum. 10 underwent to surgery including laparotomy for a positive Meckel’s scan in whom no Meckel’s diverticulum was found. Of 43 pts who were treated, 40 (93%) showed resolution of GI bleeding.

Conclusions: WCE/DBE/SBE are the best complimentary tools to investigate/treat OGIB. Despite its moderate sensitivity (67.3%), WCE is a non-invasive test that can be useful in selecting pts who need a more invasive procedure. Considering the high rate of false positivity (36%), Meckel’s scan should be considered as a secondary diagnostic option. Treatment performed according to diagnosis leads to resolution of bleeding (93%), making the case for a national centre of expertise in this area in each country.

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Role of diagnostic endoscopic ultrasound in idiopathic acute pancreatitis and acute recurrent pancreatitis in children

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**Objectives and Study:** Endoscopic ultrasound (EUS) is a minimally invasive real time pancreatic imaging modality. We evaluated the patients of Idiopathic Acute Pancreatitis (IAP) and Acute Recurrent Pancreatitis (ARP) by EUS for the changes of chronicity (Rosemont criteria). Simultaneously, the biliary factors (stone, sludge, microlith and congenital anomalies) were assessed.

**Method:** In this cross-sectional study, patients underwent EUS after 2 months of attack of pancreatitis at Paediatric gastroenterology unit of PGIMER, Chandigarh between June 2015 and November 2016. Rosemont criteria was used to classify the abnormalities seen in EUS. Yield of simultaneously performed transabdominal ultrasonography (TUS) was compared with EUS. Study plan was approved by institute ethics committee.

**Results:** Among 99 patients evaluated during study period, 45 (18 IAP and 27 ARP) underwent EUS. Mean±SD age and weight were 9.1±2.6 years and 32.66±12.43kg among IAP, whereas 12.2±3.1 years and 44.84±15.12kg in ARP. EUS demonstrated morphological abnormality in 33.33% and 40.70% of IAP and ARP respectively (p=0.61), whereas only 16.66 % and 25.92% were abnormal in TUS. Unequivocal changes suggesting chronic pancreatitis by EUS were noted only among ARP (11.11% vs. 0%). Hyperechoic ductal margin (11.10% and 18.15%) and hyperechoic foci (55.5% and 66.66%) were the most common changes seen in IAP and ARP respectively. Risk factors were identified only in ARP (25.92% vs. 0; p=0.03). Of these risk factors, sludge was the most common risk factor, seen in 18.5% (5/27), microlithiasis in 3.4% (1/27) and pancreatic divisum in 7.4% (2/27) of patients. TUS did not identify any risk factors. EUS had higher OR (95% CI) as compare to TUS to detect abnormality both in IAP [2.43(0.49-14.17); p= 0.28] and ARP [1.94 (0.60-6.47); p= 0.26].

**Conclusion:** EUS is safe and beneficial in children. One-third of IAP and ARP showed changes of chronicity. Unequivocal changes of CP (11%) and risk factors were identified only in patients with ARP. EUS performed slightly better in comparison to TUS to detect changes of chronicity.

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Severe complications after button battery ingestion in paediatrics

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Objectives and Study: Serious and fatal complications after button battery ingestion are increasing worldwide. The aim of this study is to describe (the incidence of) serious complications after battery ingestion in children in the Netherlands.

Method: All paediatric gastroenterologists performing upper endoscopies in the Netherlands were asked to report all serious complications after battery ingestion in children (0-18 years) between 2008-2016 retrospectively. Herewith, they reported the time interval between ingestion and presentation in the hospital, age and symptoms at presentation, and type and diameter of the battery.

Results: Sixteen serious complications were reported: death after massive bleeding through oesophageal-aortal fistula (n=1), oesophageal-tracheal fistula (n=5), stenosis after (suspected) perforation and mediastinitis (n=5), (suspected) perforation and mediastinitis (n=3), vocal cord paralysis (n=1) and reintubation requisite for dyspnea and stridor (n=1). The median time interval between ingestion and presentation was 5 (IQR 2-258) hours. All children were ≤5 (median 1.4; IQR 0.9-2.1) years of age. Vomiting (31.3%), swallowing/feeding problems (31.3%) and fever (31.3%) were the most common symptoms. However, 18.8% of the patients was asymptomatic (n=1 missing). All batteries were button batteries (100%) with diameters ≥20 mm in 75% and ≤20 mm (13, 15 and 17 mm) in 18.8% (n=1 missing). The batteries were removed by oesophageal gastroduodenoscopy (50%), rigid endoscopy (37.5%), or surgically (12.5%).

Conclusion: At least 16 serious complications after button battery ingestion occurred during 2008-2016 in children in the Netherlands. Serious complications were also caused by small batteries (≤20 mm) and also occurred in asymptomatic children. Therefore, immediate intervention after (suspected) battery ingestion is obligatory.
Validation of Direct Observation of Procedural Skills (DOPS) for paediatric colonoscopy

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Objectives and Study: Direct observation of procedural skills (DOPS) are tools designed by the Joint Advisory Group (JAG) to assess competence in endoscopy. These were expanded in July 2016 (new DOPS) to include those specific to paediatric colonoscopy. However, paediatric colonoscopy DOPS assessments have not been validated. Our aim was to correlate overall trainee competence with components of the paediatric colonoscopy DOPS.

Method: We performed a prospective UK-wide analysis of formative paediatric colonoscopy DOPS submitted to the JETS e-Portfolio over one-year (August 2016-2017). Scores were averaged across procedural domains (pre-procedural, procedural, post-procedural and endoscopic non-technical skills - ENTS). Each DOPS item, except for ENTS, were grouped into cognitive and technical skillsets by two independent investigators, and correlated with the overall performance score. Correlation analyses were performed using Spearman's test (rho >0.70 indicating high positive correlation).

Results: 61 DOPS assessments were completed by 13 unique trainers for 14 trainees. Overall performance score comprised: 1: Maximal supervision (1.6%), 2: Significant supervision (13.1%), 3: Minimal supervision (47.5%) and 4: Competent (37.7%). By domain, overall competence correlated most with scores for the 'Procedural' domain (rho: 0.849, p<0.001), ENTS (0.666, p<0.001), 'Post-procedural' (rho 0.635, p<0.001) and pre-procedural (rho 0.471, p<0.001). By domain, overall score correlated more with performance in predominantly 'Cognitive' (rho 0.834, p<0.001) and 'Technical' (rho 0.815, p<0.001) domains compared to ENTS. In terms of DOPS items, overall competence score correlated most with 'Proactive Problem Solving' (rho 0.836, p<0.001) and 'Patient Comfort' (rho 0.826, p<0.001), and weakest with 'Confirms Consent' (rho 0.228, p=0.115) and 'Equipment Check' (rho 0.302, p=0.020).

In summary, in colonoscopy, performance in the 'Procedural' domain, Proactive Problem Solving' items, and 'Cognitive' skill sets had greatest correlation with overall procedural competence.

Conclusion: Competencies in paediatric colonoscopy, as assessed within DOPS, vary in their correlation with overall competence. As assessors are completing the new DOPS in a consistent manner, this provides novel validity evidence for the new paediatric colonoscopy DOPS.

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Uptake of new Paediatric Direct Observation of Procedural Skills (DOPS) for OGDS

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Objectives and Study: The Joint Advisory Group on GI Endoscopy (JAG) was set up in 1994 and JAG Endoscopy Training System (JETS) went live in UK in 2009. Since 2012 Paediatric endoscopy has also been logged via the JETS system. A new Paediatric formative DOPS form was introduced in July 2016. There are currently 24 speciality trainees in Paediatric Gastroenterology, Hepatology and Nutrition and 24 General Paediatric trainees with an interest in Gastroenterology/Hepatology/Nutrition in the UK. Trainees are encouraged to fill out DOPS throughout their Endoscopy training. Adult data suggests that the new style DOPS indicate better construct validity with the new rating scale. Our aim was to survey the uptake of Paediatric DOPS forms in the 12 months following release.

Method: All Paediatric DOPS form data recorded via JETS from July 2016 - July 2017 were reviewed.

Results: 158 Paediatric OGD DOPS were recorded by 17 individuals. The number of DOPS an individual filled in varied from 1 - 24. (Mean 9.2, Mode 10).

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean DOPS per trainee (range)</th>
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<tbody>
<tr>
<td>West Midlands</td>
<td>9 (1-24)</td>
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<tr>
<td>London</td>
<td>12 (10-15)</td>
</tr>
<tr>
<td>Yorkshire</td>
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<tr>
<td>Mersey</td>
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</tr>
<tr>
<td>West Scotland</td>
<td>10(10)</td>
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</table>

[Mean number of DOPS per trainee varied between re]

Completion of DOPS forms for Paediatric OGDS varied widely between individuals and regions.

Conclusion: A more uniform uptake of Paediatric DOPS should be encouraged, perhaps by targeting the barriers to DOPS being performed that create inequalities between individuals and centres - for example some centres are not registered on JETS.

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Indications and diagnostic yield of upper gastrointestinal endoscopy in chronic kidney disease children

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Objectives and study: Gastrointestinal disorders are common (7.4% to 74%) in chronic kidney disease (CKD) patients and appear to be more frequent than in non-uremic population. Usually clinicians' threshold to perform endoscopy in those patients is high, particularly in children. This cross sectional observational study was conducted to evaluate indications and diagnostic yield of upper GI endoscopy (UGE) among grade III-V CKD children.

Methods: A total number of 125 patients with CKD stage III-V were screened for the presence of persistent or recurrent upper GI symptoms for at least 3 months. One hundred eight (86.4%) children reported upper GI symptoms; 33 patients were excluded [refusal to participate (4); confusing associated lower GI symptoms (16); other associated disorders (13)]. The remaining 75 legible CKD children (male/female = 45/30; age = 10.6±2.78 years; 33(42%) pre-dialysis; and 42(56%) on hemodialysis) were further evaluated for the presence of any indication for UGE. Twenty three patients had alarming GI symptoms and signs; but only 18 patients (endoscopy group) agreed to perform the UGE and mucosal biopsy. Helicobacter pylori stool antigen was done for all patients.

Results: The endoscopy group included 18 CKD children (male/female = 9/9; age = 13.6±2.44 years). They had significantly severe renal affection as compared with non-endoscopy group; 15 (83.3%) children stage V on hemodialysis, and 3 (16.7%) stage III predialysis patients; mean GFR was 13.2±4.4 ml/min/1.73m². The main indication for endoscopy was GI bleeding (66.7%) cases; abdominal pain and persistent vomiting in 5 (27.7%) patients; and in association with dysphagia in another I (5.6%) patient. Abnormal gross endoscopic findings were found in all cases, the most common abnormalities were in the antrum (94.4%), followed by the gastric body (83.3%) then duodenum (72.2%) and lastly oesophagus (55.6%). The most frequently reported lesions were antral nodularity (61.1%), followed by duodenal erosions (27.8%), duodenal ulcers (11.1%) and gastric erosions (11.1%). Mucosal biopsy was obtained according to modified Sydney classification in all patients except one case with active massive bleeding from duodenal ulcer that was successfully controlled with hemoclip. The reported histopathologic findings were Reflux esophagitis (76.5%); Nonspecific gastritis (70.6%); H. pylori gastritis (29.4%); Eosinophilic duodenitis (58.8%) and Nonspecific duodenitis (35.3%). Antral nodularity was not a specific sign for H. pylori gastritis [7 (58.3%) of non H. pylori cases versus 4 (80%) of H. pylori cases; p= 0.394]; while H. pylori stool antigen results matched with histopathology results with only 1 false positive case. None of the patients had reported any significant complications to UGE.

Conclusion: Upper GI bleeding is the main indication for UGE in CKD children. Antral nodularity is frequently encountered and not always a predictive sign of H. pylori gastritis. Reflux esophagitis, nonspecific gastritis and eosinophilic duodenitis are the main histopathologic abnormalities in these children.
[Endoscopic picture showing antral nodularity (a); Duodenal ulcer with hemoclip (b).]

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Urgent endoscopy in children: the proportion of a rising problem

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Introduction: Urgent endoscopy in children has specific indications, such as foreign body and corrosive ingestion, and upper or lower GI bleeding. The proportion of this problem is not clear but seem to be rising.

Methods: In order to evaluate incidence of urgent endoscopy in children we prospectively collected information about all the calls that were received during the 24 hour on-call shift for pediatric endoscopy in the region of Ile-de-France (12.1 million inhabitants) during a 6 months period (February-July 2017).

Results: A total of 237 calls (19 calls/y/100.000 children) were collected regarding children of a median age of 3.2 years (0-18). The majority of calls, 162 (68%), were for foreign body ingestion, followed by GI bleeding for 48 (20%) and caustic ingestions (19, 8%). Seventy six (32%) ended up with an urgent gastroscopy, an additional colonoscopy was performed in 7 children with GI bleeding. The endoscopy was made in 40 out of 162 foreign body ingestions (24%), 23 out of 48 GI bleeding (48%), and 12 out of 19 (63%) caustic ingestion. Foreign body extraction was done in 37 out of 40 gastroscopy (93%), an urgent oesophageal varices band ligation was performed in 3/23 (13%) GI bleeding, an additional oesophageal dilatation in 1 and the rest were diagnostic endoscopies. Median time between the call and the urgent endoscopy were below the international recommendation for disease.

Conclusions: To call the endoscopist seems to have become a recurrent practice, although in most cases urgent endoscopy does not appear necessary, especially for foreign body ingestion. Urgent endoscopic haemostasis is exceptionally needed in children. This way to organize the on call paediatric endoscopy is able to guarantee an adequate timing of urgent endoscopy in a highly populated region.

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Usefulness of the new 360° panoramic-viewing capsule endoscopy in paediatric disorders

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Objectives and Study: CapsoCam (CapsoVision Inc, Saratoga, USA) is a new small bowel capsule (SBC) with "panoramic lateral view", wire-free technology, and long-lasting recording time. It is equipped with 4 high frame rate cameras (3-5 frames/second/camera), located at the side of the capsule. Previous studies in adults, comparing this device with frontal view SBCs, showed comparable operative and diagnostic performance. There are no data in children on this technology. This is the first, single center, observational study to assess the performance of CapsoCam in children.

Methods: Between January 2016 and November 2017, consecutive children undergoing SBC with CapsoCam in single referral paediatric gastroenterology center were enrolled. All patients underwent an extensive work-up, with upper and lower gastrointestinal endoscopy. MRE was performed in all patients with suspected or established Crohn's disease (CD).

Results: Twenty-nine patients underwent SBC (median age 12 years; range 9-18). 7 (24%) were referred for suspected CD of the small bowel (SB), 15 (52%) for established CD and 7 (24%) for OGIB (3 with overt and 4 with occult GI bleeding). No technical failure was recorded. All patients excreted and retrieved the capsule. In two children the SBC was deployed endoscopically, due to the inability to swallow the capsule.
The overall diagnostic yield (rate of positive tests) was 62%: 5/7 (71%) for OGIB, 3/7 (43%) for suspected CD, and 10/15 (67%) for established CD (Table). The capsule explored the entire SB in 93% of patients. All of the recognized OGIB lesions were located in the SB: 2 angiodysplasia, 2 polyps and 1 anastomotic ulcer. In those with established CD (n = 15), SB lesions were revealed by MRE in 7 and by SBC in 10 patients, respectively. Of 7 patients with suspected IBD, SB lesions typical of Crohn's disease were observed in 3 with SBC vs 1 with MRE. The SBC identified upper and/or lower GI tract lesions in 36% of patients with suspected or established CD.
Bowel preparation was adequate in 86% of the procedures. No serious adverse event was recorded during the study. Twenty-seven (93%) of patients considered SBC tolerable and would undergo the procedure again.

Conclusions: This first observational paediatric study suggests that CapsoCam is a safe and tolerable procedure in children, with a detection rate comparable to other SBC with frontal view. Further studies are necessary to explore and expand the capabilities and usefulness of this device.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>12 (9-18)</td>
</tr>
<tr>
<td>Indications: - Suspected CD</td>
<td>7 24%</td>
</tr>
<tr>
<td>- Established CD</td>
<td>15 52%</td>
</tr>
<tr>
<td>- OGIB</td>
<td>7 24%</td>
</tr>
<tr>
<td>Diagnostic yield: - Overall</td>
<td>18/29 62%</td>
</tr>
<tr>
<td>-Suspected CD</td>
<td>3/7 43%</td>
</tr>
<tr>
<td>-Established CD</td>
<td>10/15 67%</td>
</tr>
<tr>
<td>-OGIB</td>
<td>5/7 71%</td>
</tr>
<tr>
<td>Endoscopic placement</td>
<td>2 7%</td>
</tr>
</tbody>
</table>

Disclosure of interest: Salvatore Oliva received lecture fees from Capsovision
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Pediatric upper gastrointestinal bleeding in children: Etiology and treatment approaches

Esra Polat¹, Nevzat Aykut Bayrak¹, Günsel Kutluk¹, Hasret Civan Ayyildiz¹, Hatice Baba¹

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Objectives and Study: Upper gastrointestinal bleeding (UGB) is one of the most serious cause of admission to the hospital in childhood. Besides, diagnosis and treatment is a challenge for pediatric gastroenterologists. The frequency of pediatric cases is unknown, although, it is estimated that in approximately 20% of the pediatric patients, the source of the gastrointestinal bleeding is the upper gastrointestinal system. Understanding the cause and correcting with an appropriate therapeutic approach are the key in the management of UGB.

Method: The aim of the study is to evaluate the etiological factors and the treatment approaches in patients with UGB. In this multicenter, cross sectional study, UGB cases admitted to emergency clinic, were evaluated between January 2014 - August 2017.

Results: There were 198 children (50.5% male, mean age:9.42±5.3 years) admitted to pediatric emergency clinic. In 14.6% (n=29) patients NSAID history was present. Esophagitis was found in 93 (47%) patients, esophagus varices were detected in 22 (11.1%) patients. Peptic ulcer was found in 36 (18.1%) patients; it was localized in corpus, antrum or bulbous respectively (5 (2.5%), 17 (8.5%), 14 (7.1%)). H. Pylori (Hp) was found in 122 (61.7%) patients (antrum 46.4% vs corpus 25.3%, p&LT; 0.05). The frequency of chronic liver disease was 12.6%. Erythrocyte transfusion (ET) was ordered in 29 (14.6%) patients. Twenty cases (10.1%) received octreotide infusion. In 22 (11.1%) patients, an endoscopic therapeutic approach was necessary: band ligation therapy (n=5), sclerotherapy (n=7), adrenaline injection (n=10). Therapeutic interventions were applied significantly for esophageal varices or peptic ulcer in bulbous (p&LT; 0.01). In contrast to non-Hp associated peptic ulcer cases, Hp-associated peptic ulcer cases required endoscopic therapeutic intervention (p&LT; 0.01). The ET administration rate was higher in cases who presented with both melena and hematemesis, in comparison with cases who had only melena or hematemesis (p&LT; 0.001). Eightyfour (42.4%) patients were hospitalized, mean hospitalization time was 2.73±1.18 days. ET administration requirement was correlated with hospitalization time (r²=0.68, p&LT; 0.01).

Conclusion: Our multicentric cohort shows that, although UGB is an uncommon entity among all pediatric emergency admissions, serious conditions such as esophageal variceal bleeding and peptic ulcer might be life-threatening and is associated with endoscopic therapeutic intervention requirement, ET administration and longer hospital stay.

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Prevalence, risk factors and management of anastomotic stricture formation after oesophageal atresia repair: a multicentre study

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Objectives and Study: To determine the prevalence of anastomotic strictures after oesophageal atresia (OA) repair, to identify risk factors associated with refractory stricture formation and to evaluate its management.

Methods: Retrospective study in OA patients born between 1999-2013, treated in five centres in the Netherlands. Exclusion criteria were isolated fistula, inability to obtain oesophageal continuity, death prior to discharge and follow-up < 6 months. A refractory oesophageal stricture was defined according to the recent ESPGHAN guideline1 as an anastomotic stricture requiring ≥5 dilations at maximally four-week intervals. A clinically relevant oesophageal stricture was defined as an anastomotic stricture requiring ≥3 dilations. Risk factors for development of refractory anastomotic strictures after OA repair were identified with multivariable logistic regression analysis. Ethics approval was obtained.

Results: We included 454 children (61% male, 7% Gross type A) with end-to-end anastomosis performed in 436 (96%). Anastomotic leakage occurred in 13%. Fifty-eight percent of children with an end-to-end anastomosis developed an anastomotic stricture, requiring a median of 3 (range 1-34) dilations. Balloon dilatation was applied in 28.6% of dilatations, bougienage was used in 68.1% of dilatations. In the remaining 3.3% type of dilatation was unknown. Refractory strictures were found in 32/436 (7%) children and required a median of 10 (range 5-34) dilations. Clinically relevant oesophageal strictures were defined as an anastomotic stricture requiring ≥3 dilations. Risk factors for development of refractory anastomotic strictures after OA repair were identified with multivariable logistic regression analysis. Ethics approval was obtained.

Table 1: Multivariable logistic regression analysis for refractory anastomotic stricture (≥5 dilations) and clinically relevant anastomotic stricture (≥3 dilations) in children with oesophageal end-to-end anastomosis (N=436)
<table>
<thead>
<tr>
<th></th>
<th>≥5 dilations</th>
<th></th>
<th>≥3 dilations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p-value</td>
<td>OR</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.98</td>
<td>0.85-1.12</td>
<td>0.711</td>
<td>0.96</td>
</tr>
<tr>
<td>Gross type A</td>
<td>5.71</td>
<td>1.48-22.13</td>
<td><strong>0.012</strong></td>
<td>5.79</td>
</tr>
<tr>
<td>Thoracosopic repair</td>
<td>0.45</td>
<td>0.14-1.50</td>
<td>0.191</td>
<td>0.72</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>5.03</td>
<td>1.88-13.43</td>
<td><strong>0.001</strong></td>
<td>2.93</td>
</tr>
<tr>
<td>Dilation ≤28 days</td>
<td>15.90</td>
<td>5.89-42.92</td>
<td><strong>&lt;0.001</strong></td>
<td>10.59</td>
</tr>
</tbody>
</table>

[Multivariable logistic regression analysis]

**Conclusion:** The incidence of refractory stricture formation in end-to-end anastomosis in children treated for OA was 7%. Risk factors were OA Gross type A, anastomotic leakage and the need for oesophageal dilation within 28 days after OA repair. Children showing one or more of these factors may benefit from supportive care (e.g. adequate acid suppression) aimed at preventing the development of a severe refractory stricture. Further research to additional treatment options (e.g. stents, mitomycin, intralesional steroid injections) could be useful in prevention of refractory stricture formation.


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Spontaneous esophageal perforation in paediatric age

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Objectives and Study: The spontaneous esophageal perforation is a rare devastating condition. The lethal perforation of the gastrointestinal tract is usually diagnosed incidentally in a patient complaining about chest pain.

Methods and Results: A 15 years old male, previously healthy, started a 9 days course of bloody diarrhea, associated with dysphagia and right thoracoabdominal 5 days after the onset. Firstly observed in his hospital nearby, where the blood tests showed anemia, leukocytosis and an elevated C-reactive protein (CRP). After a normal chest and abdominal X-Ray he was transferred to our hospital to perform an endoscopic study. In the previous 20 days he lost 2 kilograms. An isolated peak of fever registered the day before he came to the hospital. There was no history of recent nausea, vomits, heartburn or infections. Although in his early childhood vomits were frequent and since he was 6 years old, common impactions episodes occurred, understood by the patient to be related with anxiety. He presented anemia (12.2g/dl), leukocytosis (15700/uL) and CRP of 120mg/dl. In the upper digestive endoscopy, there was an esophageal 32 mm hole in the distal portion, on the left lateral strand, with purulent content extravasation, compromising the continuity of the procedure. He was admitted to the pediatric intermediate care unit and a computed tomography (CT) was performed to confirm the previous finding. Mediastinitis was excluded. He started ceftriaxone, metronidazole as well as pantoprazol. A 3410ug/g fecal calprotectin and ANCA MPO positive were found in the first laboratory tests. Once there was positivity for herpes I serology, he initiated acyclovir, until the exclusion of the suspicion of herpetic esophagitis. Parenteric nutrition was instituted. A rectosigmoidoscopy was performed the day after, with biopsy showing an acute colitis, and negativity for cytomegalovirus and herpes I and II. The rectal bleeding and diarrhea persisted, as well as the weight loss. Since the strong suspicion of inflammatory bowel disease, he started polymeric diet 15 days later. An ulcerated lesion of the tonsillar pillar was found in the patient, which biopsy showed an epithelioid granuloma, allowing diagnosis of Crohn's disease. On the 13th day in the Magnetic Resonance Enterography, the esophageal perforation was resolved. Therefore, the endoscopic study could be repeated resulting in ileocolitis compatible with Crohn's Disease. In the esophagus biopsy, there were more than 15 eosinophils/hpf, diagnosing eosinophilic esophagitis. Given the findings he was prescribed fluticasone. The patient refused to continue with the polymeric diet, thus, prednisolone and azathioprine were started before the general diet. On the 23rd day of admission the stools were more consistent and less frequent, still with traces of blood in them. Once the clinical and analytical outcomes were favorable, he was discharged, with continued care from the Paediatric Gastroenterology Unit. Conclusion: The majority of esophageal perforations were due to some enteric instrumentation complications. However, as incidences of eosinophilic esophagitis appear to be increasing, the pediatric gastroenterologist should be alert to the possibility of an esophageal perforation in similar circumstances, avoiding severe clinical complications.

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Carbon dioxide insufflation during colonoscopy in deeply sedated pediatric patients decrease narcotic usage and post-interventional abdominal discomfort: A prospective randomized controlled trial

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The usage of carbon dioxide (CO₂) instead of room air (RA) during colonoscopy of adults revealed significantly less flatulence and abdominal pain in several studies. The aim of this study was to investigate the effects of CO₂ usage on post-interventional pain, abdominal discomfort, abdominal girth, pCO₂ levels and narcotic requirement in deeply sedated pediatric patients. The study was a prospective randomized, single blinded, controlled trial (RCT) approved by the institutional review board of Ulm University, Germany. A total of 73 children and adolescents ranged between 4 and 17 years undergoing colonoscopy for various indications were randomized to RA or CO₂. Abdominal pain was assessed 15 minutes before the examination and 15, 60 and 180 minutes and 24 hours afterwards by an age appropriate 10-point visual analogue scale (VAS), combining numerical rating scales, a colored analog scale and a face pain scale. In addition, abdominal girth, transcutaneous pCO₂, narcotic requirement to achieve deeply sedation and post-procedural analgesic demand was assessed. Overall significantly less patients reported abdominal pain in the CO₂ group and we observed a trend to lower post-interventional pain documented 1, 3 and 24 hours by VAS score. In addition, patients receiving CO₂ reported significantly less bloating (p=0.0007), but did not differ in abdominal girth. There was no significant difference in the transcutaneous pCO₂ values in both groups and no pathological pCO₂ increase occurred in the carbon dioxide group. Despite there was no difference in the dosage of propofol and midazolam we observed an significant increased necessity of additional synthetic opioid usage in the room air group (61.8%) compared to the carbon dioxide group (38.5%) to achieve optimal examination conditions. In conclusion, the benefits using carbon dioxide in colonoscopy of deeply sedated children predominate. In particular, CO₂ insufflation allows a less painful post-interventional time in children and abdominal bloating was significantly reduced. Moreover, significantly less opioids were used for sedation using carbon dioxide. Carbon dioxide insufflation can be considered as save in deeply sedated patients as there was no relevant pulmonary CO₂ retention observed. Therefore, carbon dioxide instead of room air should be recommended for endoscopy in children.

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Dysphagia and food impaction secondary to Schatzki Ring in a paediatric patient

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Objectives and Study: To describe the clinical presentation of a paediatric patient with Schatzki Ring (SR).

Method: A case report of a patient with SR who received care at the Instituto Nacional de Pediatría (INP) in México City.

Results: A 2-year-old female, previously healthy, was referred to the Paediatric Gastroenterology department because of a 1-year history of undigested food vomiting, accompanied by dysphagia—mainly to solid foods. Physical exam was normal. During hospitalization the patient underwent a barium esophagram, which showed 39 mm narrowing at the distal third portion, approximately 30 mm above the oesophageal hiatus (panel A). High resolution oesophageal manometry was performed, which ruled out oesophageal achalasia; 24-hour pH Impedance test showed acid Gastroesophageal Reflux Disease (GERD). The patient was readmitted to the hospital because of acute severe dysphagia. Panendoscopy was performed with a paediatric Olympus GIF Q-150 endoscope (9,2 mm), which showed food lodged at the distal third portion of the oesophagus and a concentric, fine circular mucosal fold approximately 2.5 cm above the squamocolumnar junction (panel B). Biopsies from the oesophageal narrowed portion (distal third portion) showed moderate active-chronic peptic esophagitis, and mild-chronic esophagitis at the proximal- and medium-third portion without eosinophilic infiltration. During hospitalization, the patient had two acute food oesophageal impaction episodes that required foreign body extraction by endoscopy. The patient was treated with esomeprazole (2 mg/kg/day), cisapride (0.25 mg/kg/day) and soft food diet. Currently, the patient is asymptomatic showing good response to treatment.
Conclusion: SR usually presents in patients older than 40 years. Only a few cases of SR in paediatric patients have been reported in the medical literature. SR is a 1-4 mm circumferential submucosal ring located at the distal third portion of the oesophagus; usually accompanied by hiatal hernia. The presence of dysphagia and recurrent food impaction accompanied by undigested food vomiting in children and young patients must raise suspicion of the following diagnoses: GERD, oesophageal stenosis, achalasia, eosinophilic esophagitis and SR. The presence of recurrent food impaction is highly associated with eosinophilic esophagitis, however, SR must also be considered in the differential diagnosis. Esophagram obtained with the prone and oblique position views has a high sensitivity. In the case of our patient, hiatal hernia and achalasia were ruled out by high resolution manometry and endoscopy, and acid GERD was confirmed by 24-pH impedance. The aetiology of SR is unknown. Three aetiological hypotheses have been proposed: congenital, anatomical and inflammatory. The inflammatory hypothesis associated with GERD is the most widely accepted. Given the young age and the presence of GERD in our patient, we believe the aetiology of SR may be congenital/inflammatory associated with GERD.

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Novel techniques in endoscopic jejunal tube placement

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Objectives: Jejunal feeding tubes are becoming increasingly used to address nutritional needs in those children who require post-pyloric feeding, especially those with neurodisability associated GI dysmotility. These tubes can be placed surgically or endoscopically or under radiological guidance. Percutaneous endoscopic gastro-jejunostomies (PEGJ) are not without a potentially prolonged endoscopy time or procedure failure and are associated with post-procedural complication compared with PEG feeding tubes. This may include tube displacement, malfunction or breakage. We present a small case series of the use of the Boston Endoclip to tether the jejunal tube in position during PEG-J insertion to demonstrate this as a novel, safe and effective method, which potentially can reduce the associated complications.

Method: We retrospectively reviewed electronic theatre documentation, patient notes and radiological records of five children who had undergone a PEGJ insertion using a Boston Endoclip when placing the jejunal feeding tubes. We concentrated on patient demographics and indication for PEGJ, intra-operatively complications and 6 and 12 month follow up. We also looked at whether they had later undergone any surgical interventions.

Results: All five children underwent this procedure, performed by one endoscopist, between 2013-2015. All children successfully underwent the insertion of a 16Fr PEGJ using the Boston Endoclip to fix the jejunal extension to the mucosal wall. This Endoclip normally used in endotherapeutics such as GI Bleeding provides the jejunal tube with a temporary fixed position before falling off some days later. Our five patients (3Male) were between 7-75 months of ages. Indications included suspected foregut dysmotility (4) vomiting on gastric feeding (3) severe GORD; unsuitable for fundoplication (2); unsafe swallow (2) and failure to thrive (1). 80% had a diagnosed underlying neurological condition. The procedure time ranged from 19-26minutes (median 23). Two had minor bleeding in the duodenum attributed to trauma from the endoclip. No patients required intervention for bleeding. At six month follow up only 1 child had required a non-elective PEGJ reinsertion which was done under radiological guidance. Another child required admission and investigation for bilious vomiting but did not require intervention, and vomiting resolved spontaneously. At 12months 2 patients had required a further unplanned radiological PEGJ insertion for displaced jejunal tubes and one received contrast via the PEGJ after presenting with vomiting but the tube was found to be in the correct position. This accounts for four episodes of tube related complications over a 12 month period. 4 of 5 patients underwent a surgical intervention within the total follow up period, two of which were laparoscopic assisted PEJ insertions. Two patients no longer required post-pyloric feeding and PEGJ was converted to a Gastrostomy.

Conclusion: In summary, the Boston Endoclip is a novel technique for the insertion of jejunal feeding tubes in those undergoing PEGJ. It has proven to be safe and has demonstrated intraoperative efficacy in this small cohort and may be associated with reduced jejunal tube displacement.
Objective: Obscure GI Bleeding in Children poses multiple diagnostic challenges, frequently presenting to other centres prior to tertiary paediatric gastroenterology services. Despite advances in endoscopic investigations and techniques, the clinical complexity and mortality remains high. We present our 7 year experience on the management of obscure GI bleeding (OGIB) in children as a leading paediatric endoscopy centre.

Subjects and Methods: We reviewed the notes of paediatric patients with OGIB who underwent diagnostic evaluation and management in our centre from 2010-2017.

Results: 15 patients (7M) aged 2-16y were identified. The primary GI bleeding presentation included haematochezia (6), melaena (7) and haematemesis (3). Two patient's required resuscitation because of collapse secondary to GI bleed. A fifth complained of recurrent abdominal pain. 100% of patient's had already undergone upper GI endoscopy +/- ileocolonoscopy prior to referral; 60% of those within in tertiary GI centres.

Investigations had already been extensively performed at local centres:
- Wireless capsule enteroscopy (WCE) (5)
- Meckel's scan (2)
- CT angiogram (2)
- Technetium-99m red blood cell scan (1)
- Laparotomy (2)
- Laparoscopy (2)

A third of patients received blood transfusions (one being transfusion dependent for 10 years) and over 25% had refractory iron deficiency anaemia at referral. Initial treatment at local centres included ocreotide/terlipressin in 25%. Three patients had undergone colonic resection under the paediatric surgeons because of persistent anaemia secondary to occult GI losses. No children in this cohort died.

Time taken from initial presentation to review within our centre ranged from 4 days to 10 years (median 16m). 100% of patients underwent endoscopic re-assessment with upper GI endoscopy and ileocolonoscopy in our unit. Early liaison with clinical geneticist provided diagnosis in 2 patients, which directly influenced maintenance therapy. Further investigations performed by our centre included:
- WCE (13),
- Antegrade and retrograde double balloon enteroscopy (DBE) (8)
- Laparoscopic assisted enteroscopy (4)
- CT angiography (1)
- CT abdomen (1)
- Meckel's scan (1)

A summary of 12 of these patients are listed below (Image 1)
In 2 patients the site of GI bleeding was not identified; in one the bleeding was attributed to severe oesophagitis, the other was later found to be self-harming with induced or fabricated GI bleeding.

**Conclusion:** The site of GI bleeding was identified in 80% of the cases, the cause of which was determined in all 15 patients. Advances in small bowel imaging with WCE, DBE, radiological imaging as well as a strong professional relationship between gastroenterologists and surgeons have enhanced the diagnostic evaluation and treatment of this complex presentation. The management of OGIB in children can be effectively managed and mortality reduced in centres where these specialist experiences exist.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Modality</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 Concentric stenosis and ischaemic, non-specific ulceration in small bowel</td>
<td>Lap-Assisted Enteroscopy</td>
<td>SLCO2A1, resection, Azathioprine</td>
</tr>
<tr>
<td>Patient 2 Blue Rubber Bleb Nevus (gastric body)</td>
<td>Upper GI endoscopy</td>
<td>Argon plasma coagulation, endoclips, proximal gastrectomy</td>
</tr>
<tr>
<td>Patient 3 Apthoid ulcers (distal ileum)</td>
<td>DBE</td>
<td>Treatment for Crohn’s disease</td>
</tr>
<tr>
<td>Patient 4 Polyps in small bowel (Peutz-Jeghers)</td>
<td>WCE</td>
<td>Polypectomy/endoclips</td>
</tr>
<tr>
<td>Patient 5 Angiodysplastic lesions (colon)</td>
<td>Colonoscopy</td>
<td>Referral for resection</td>
</tr>
<tr>
<td>Patient 6 Meckel’s diverticulum</td>
<td>Lap-Assisted Enteroscopy</td>
<td>Excision</td>
</tr>
<tr>
<td>Patient 7 Perforated gastric duplication cyst with transverse colon fistula</td>
<td>CT abdomen</td>
<td>Resection</td>
</tr>
<tr>
<td>Patient 8 Threadworms in small bowel</td>
<td>DBE</td>
<td>Mebendazole</td>
</tr>
<tr>
<td>Patient 9 Meckel’s diverticulum</td>
<td>Lap-Assisted Enteroscopy</td>
<td>Excision</td>
</tr>
<tr>
<td>Patient 10 Lymphangiectasia</td>
<td>DBE</td>
<td>Conservative treatment</td>
</tr>
<tr>
<td>Patient 11 Jejunal varices</td>
<td>DBE</td>
<td>Banding</td>
</tr>
<tr>
<td>Patient 12 Polyps in the colon and small bowel</td>
<td>Colonoscopy</td>
<td>Polypectomy/Sirolimus</td>
</tr>
</tbody>
</table>
Anemia and gastrointestinal endoscopy in children

Marleena Repo¹, Antti Sotka², Pauliina Hiltunen³, Katri Kaukinen¹, Katri Lindfors¹, Kalle Kurppa²

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²Tampere Centre for Child Health Research, Tampere, Finland
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Objectives and Study: Gastrointestinal diseases are regarded as a common cause of pediatric anemia, but the outcomes and long-term prognosis of anemic children undergoing endoscopic investigations are poorly known. We explored these issues in a large cohort of children presenting with anemia in a tertiary referral center.

Methods: Medical data from 1146 children having undergone gastrointestinal endoscopies was available for the study. Comparisons between anemic and non-anemic patients as well as between anemic patients who did and did not reach a final diagnosis were made. Follow-up data was available up to 10 years.

Results: Altogether 737 patients had a known hemoglobin value at the time of first endoscopy, of whom 222 (30.1%) were anemic. The medium hemoglobin value in the anemic patients was 107 g/l and in the non-anemic patients 131 g/l (p< 0.001). Anemic children had more often bloody diarrhea (21.9% vs 9.1%, p< 0.001), poor growth (12.9% vs 6.4%, p=0.021) and weight loss (18.3% vs 8.2%, p< 0.001) and less often abdominal pain (54.9% vs 67.4%, p=0.002), reflux (10.3% vs 17.3%, p=0.010) and dysphagia (0.9% vs 4.5%, p=0.013) than those without anemia. They also received more often diagnosis in endoscopy (76.6% vs 51.8%, p< 0.001), the most common of which were celiac disease (28.4% vs 20.2%, p=0.017) and inflammatory bowel disease (30.7% vs 9.7%, p< 0.001). Factors predicting the diagnosis were bloody diarrhea and positive celiac serology. Unexplained anemia was the sole reason for endoscopy in 30 children in whom 19 received diagnosis, most frequently celiac disease (n=13). During the later follow up a diagnosis was received by five anemic patients presenting with other symptoms and by none of the patients with anemia only.

Conclusions: Anemia increases the probability of a diagnosis in gastrointestinal endoscopy, the most common findings being celiac disease and inflammatory bowel disease. Our results emphasize the importance of anemia as an alarm symptom in these diagnostic scenarios. Endoscopy should be considered with low threshold even in children with persistent anemia as the sole symptom.
Gastrointestinal endoscopy
N=1590

Diagnostic endoscopy
N=1146

Diagnostic endoscopies with anemia data\(^1\)
N=737

Follow-up endoscopy
N=444

Insufficient data
N=408

No anemia
N=515

Anemia
N=222

Also other symptoms
N=192

Only anemia
N=30

No diagnosis
N=41

Diagnosis
N=151

Later diagnosis\(^2\)
N=5

No diagnosis
N=36

Total diagnoses
N=156

Diagnosis
N=19

Later diagnosis\(^3\)
N=0

No diagnosis
N=11

Total diagnoses
N=19

No diagnosis
N=11

\(^1\) A patient was considered anemic if his/her hemoglobin was below age-dependent reference values at the time of endoscopy.

\(^2\) During the follow up until February of 2017.

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Association of upper gastrointestinal symptoms, endoscopic and histopathological findings in children

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Objectives and Study: The aim of our study is to determine the relationship between upper gastrointestinal (UGI) symptoms, endoscopic and histopathological findings of the oesophagal and gastric mucosa in children who underwent esophagogastroduodenoscopy (EGD).

Methods: The medical charts of 884 patients who underwent EGD, aged 4-18 years old, were reviewed retrospectively for demographic characteristics, UGI symptoms, endoscopic and histopathological findings.

Results: Out of 884 patients (63.2% females), with a mean age of 12 ± 3.8 years (4 - 18 years), 674 (76.2%) had UGI symptoms with a significant female predominance (female/male ratio: 1.9/1) (p<0.0001). Patients with upper GI symptoms were significantly older than the patients without symptoms (p< 0.0001). Abnormal endoscopic appearance of the oesophagus and gastric mucosa were more frequent in patients with UGI symptoms (p<0.0001, p<0.0001 respectively), however in histopathological examination only antral mucosal abnormalities were frequent in patients with UGI symptoms (p=0.03). Epigastric pain, nausea, and vomiting were significantly more frequent in patients with oesophagal abnormalities on endoscopy. There was a significant relation between endoscopic and histopathological findings of antral and corpus mucosa in all patients, but this relationship was only seen in patients with UGI symptoms on oesophagus mucosa. Helicobacter pylori infection wasn't related to any of the UGI symptoms, bile reflux and oesophagitis. Bile reflux was significantly related to epigastric pain (p<0.001) and nausea (p<0.001). The positive predictive value of endoscopic findings controlled with histopathological findings were 54.3% for oesophagus and 34.1% for gastric mucosa.

Conclusions: Although there was a significant relationship between endoscopic and histopathological findings of patients, due to the low positive predictive value of endoscopic evaluation, taking multiple biopsies may be beneficial.

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The pull-introducer technique in small infants: describing our centre experience in 3 children

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Objectives: Kirberg A described in 2016 a new technique for gastrostomy tube placement small for gestational age newborns. The classic pull-through technique, passing a 15 mm bumper through a small oesophagus (5-8 mm) can be troublesome. On the other hand the one-step balloon gastrostomy requires stomach fixation with large fixators and tract dilatation which are not designed for the small infants. The technique described by Kirberg combines 2 endoscopic techniques. Our experience with the technique in 3 small infants requiring a gastrostomy tube in combination with a Nissen fundoplication, is described.

Method: After the laparoscopic Nissen fundoplication, a classic pull technique PEG gastrostomy 14 Fr is placed. However, although the pointed end is pulled through the abdominal wall, the tube bumper is stopped at the mouth of the patient. A 10 Fr balloon gastrostomy is then pushed into the PEG 14Fr, as if it was a guidewire. The gastrostomy is pulled back under endoscopic view. When the balloon gastrostomy is in place, the PEG gastrostomy is removed by firmly pulling the oral end. The balloon is filled and the tube fixed with 2 sutures to prevent early removal.

Results: Three infants (weight 4000-6000 gram) needed a gastrostomy and Nissen fundoplication. They had an important anaesthetic risk for which a one-step balloon gastrostomy was preferred. After parental consent the new method was chosen since the one-step balloon gastrostomy gastropexy devices were estimated to be too large for these infants. No immediate nor long-term complications (including local infection) were registered. All 3 infants were dismissed from the hospital as planned. After 6 months the balloon gastrostomy was changed for a 12 Fr 1.5 cm button in one patient and a new 10 Fr balloon gastrostomy in the others.

Conclusion: In infants with a low weight, the new method ‘pull-introducer’ seems very promising. The advantage of using a classic technique that is familiar to all endoscopic professionals is huge. It felt safe and easy to perform. One-step placement of a balloon gastrostomy was successful in all 3 infants without complication.

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Unexpected endoscopic findings in a group of children with type 1 diabetes

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Objectives and Study: Association between type 1 diabetes (T1D) and autoimmune atrophic gastritis is well known. The aim of this study was to identify endoscopic features and prevalence of characteristic gastroscopic picture of atrophic gastritis in a group of children with type 1 diabetes.

Method: We reviewed the findings from endoscopy in a group of children with type 1 diabetes who were admitted to the Rauchfuss Children’s Hospital, Saint-Petersburg over a six-year period. A total of 64 children (46 girls and 18 boys) with T1D were studied. 64 healthy children presented comparison group. All patients underwent upper gastrointestinal endoscopy with rapid urease test.

Results: Upper endoscopy detected erosive antral gastritis in 26% (17) of the patients with diabetes and in 2% (3) of healthy controls (p< 0,001). The rate of H. pylori infection in children with diabetes was 72% (46) and 64% (41) in healthy children. There was no statistically significant difference (p>0.05) in the incidence of H. pylori infection between main group and comparison group, proving that H. pylori infection did not cause gastric erosions in patients with type 1 diabetes. Nodular antral gastritis was observed in 11% (7) children of control group in comparison to 1% (1) of children of main group (p<LT; 0,05).

Conclusion: We did not found characteristic gastroscopic picture of atrophic gastritis in children with T1D. Further studies are needed to evaluate causes leading to erosive antral gastritis in children with type 1 diabetes.

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Microvillus inclusion disease: an experience from a single tertiary care center-KFMC-Saudia Arabia

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Objectives and Study: Microvillus inclusion disease (MVID) is a rare autosomal recessive enteropathy, characterized by severe intractable diarrhea that results in intestinal failure and malnutrition. Histology showed villous atrophy with an increased number of secretory granules within enterocytes and membrane-bound inclusions. Mutations in MYO5B gene and syntaxin 3 (STX) had been identified as causes of classic MVID and MVID-variant respectively. The objective of this study was to analyze the clinical feature, diagnosis as well as outcome of patients affected by the disease.

Method: Retrospective chart review from 2006 to 2017 was performed in 10 infants diagnosed with MIVD based on histopathology and gene test. The recorded parameters included a clinical feature, diagnosis, and outcome.

Results: All patients were from consanguineous families. The onset of diarrhea was in an early neonatal period in all patients. One patient was weaned off PN. One patient underwent SBTx. Four patients are PN dependent, and four died between (4 months - 7 years of age). One patient had subtle dysmorphism with hyperpigmentation and wooly hair. Two patients (sibling) experienced chronic and recurrent low GGT cholestasis, not related to PN. All patients remained stunted in spite of adequate calories provided by PN. PN related liver, bone and renal diseases were commonly seen. One patient had pseudo intestinal obstruction -like disease and spontaneous small intestinal perforation. Intestinal histology including electron microscopy (EM) findings were consistent with MVID in all patients, except one. Different MYO5B mutations were detected in 7 families, and a homozygous mutation in (STX 3) gene was identified in one patient.

Conclusion: The main presentation of MVID is severe, life-threatening diarrhea. However, it may have diversity in phenotypic expression. Metabolic bone disease, stunted growth, nephrocalcinosis and vascular thrombosis are common complications seen in our cohort. The mortality rate is still high with current therapies. However, future innovative therapeutic technology such as gene editing might be curative.

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Infantile systemic hyalinosis presenting with intestinal lymphangiectasia

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Objectives and Study: Infantile systemic hyalinosis (ISH) is a very rare disorder characterized by progressive joint contractures, skin abnormalities, severe chronic pain and widespread deposition of hyaline material in many tissues such as the skin, skeletal muscle, gastrointestinal tract. Herein, we report a 6-months-old boy with ISH presenting with protein loosing enteropathy (PLE) due to intestinal lymphangiectasia.

Results: His symptoms had started shortly after birth with deformity of extremities. During follow up period repetitive physical examinations revealed severe contractures in ankle, knee, hip, wrist and elbow joints bilaterally, gingival hypertrophy, multiple papules over his ears, neck and perianal region. Esophagastroduodenoscopy was performed for diarrhoea and hypoalbuminemia revealed diffusely elongated, circumferential and polypoid mucosae covered with whitish enlarged villi, all of which indicate intestinal lymphangiectasia. Histopathological evaluation of duodenal tissue samples revealed focal villous atrophy, perivascular hyalinosis and lymphangiectasia. Skin biopsy from neck demonstrated pink homogeneous acellular material throughout the dermis suggestive of hyalin. Anthrax toxin receptor 2 (ANTXR2) gen sequence analysis revealed homozygous IVS11-1G>A (c.946-1G>A) mutation.

Conclusion: Because of hyaline deposition in intestinal walls, these patients have diarrhoea that lead to failure to thrive and severe malnutrition as it was observed in our patient. However, beside perivascular hyalinosis we also demonstrated intestinal lymphangiectasia which was reported up to date only in one infant with ISH. There is no specific treatment for ISH. Dietary modifications with high protein, MCT oil, and vitamin supplements remain the mainstay of management in patients with lymphangiectasia.

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Objectives and Study: Intractable diarrhea of infancy (IDI) is a group diarrheal disorders that is difficult to diagnose and manage. It persists longer than 2 weeks. Despite detailed laboratory examinations, the diagnosis can be only made with genetic analysis in some cases. Herein; we aimed to analyse the general features, causes, genetic results (in studied patients) and outcome of the patients with IDI in our center since 2007.

Method: The study included 46 patients hospitalized for IDI ages 0 to 24 months in our center. Detailed history, laboratory parameters, genetic analysis, diagnosis and outcome were recorded.

Results: The male/female ratio was 1.09. The median age at onset of diarrhea was 45 days (range 1 to 192 days). Chronic malnutrition was present in 36.9% of the patients. Anemia, hypoalbuminemia and acid-base disturbance at initial admission was found in 78.2%, 39.1% and 36.9% of the patients, respectively. Other systems involvement including renal, skin, neurological, hepatic and cardiac involvement were found in 10.8%, 8.7%, 21.7%, 8.7% and 2.1% of the patients. Causes of IDI were carbohydrate malabsorption in 2 (4.3%), congenital enterocyte/enteroendocrine differentiation defect in 4 (8.6%), early onset IBD in 3 (6.5%), fat malabsorption in 6 (13%), food allergy in 11 (23.9%), short bowel syndrome in 6 (13%), celiac disease in 7 (15.2%) and 1 (2.1%) for each; chronic intestinal pseudoobstruction (CIP), autoimmune enteropathy (AE), primary intestinal lymphangiectasia, HIV infection, familial hemophagocytic lymphohistiocytosis type 5, undefined immune deficiency and undefined etiology. The diagnosis of the etiological factor was confirmed by genetic analysis in 9 cases (Table 1).

<table>
<thead>
<tr>
<th>CAUSES of IDI</th>
<th>GENE</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron retention disease</td>
<td>SAR1B gene</td>
<td>homozygous c.142delG mutation</td>
</tr>
<tr>
<td>Johanson-Blizzard syndrome</td>
<td>UBR1 gene</td>
<td>homozygous c.497A&gt;G mutation</td>
</tr>
<tr>
<td>Familial hemophagocytic</td>
<td>STXB2 gene</td>
<td>homozygous IVS10+5G&gt;A (c.902+5G&gt;A) mutation</td>
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<tr>
<td>lymphohistiocytosis type 5</td>
<td></td>
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<tr>
<td>Tricho-hepato-enteric syndrome</td>
<td>TTC37 gene</td>
<td>homozygous c.2122C&gt;T (p.Gln708)</td>
</tr>
<tr>
<td>Microvillus inclusion disease</td>
<td>MYO5B gene</td>
<td>Homozygous c.2014A&gt;T (p.K672X) mutation</td>
</tr>
<tr>
<td>Cystic fibrosis + Barth syndrome</td>
<td>CFTR and TAZ gene</td>
<td>V754M/c.1408 G&gt;A and C51.G&gt;C (p.Trp17X)</td>
</tr>
<tr>
<td>Very early onset IBD (FMF)</td>
<td>MEFV gene</td>
<td>homozygote M694 V mutation</td>
</tr>
<tr>
<td>Proprotein convertase 1/3</td>
<td>PCSK1 gene</td>
<td>homozygous splice-site mutation, c.544-2A&gt;G</td>
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<td>deficiency</td>
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[Genetic study of the patients]

Treatment modalities were prolonged TPN (range; 1 months - 2 years) in 11 patients (23.9%), diet modifications in 25 (54.3%), immunosupression in 6 (13%) and supportive medication in 7 patients (15.2%). 3 patients (6.5%) underwent enteroplasty operation. The median duration of hospitalization was 48 days (range; 2 days - 2 years). 6 patients (13%) died during the follow-up period; 1 for each;
CIP, AE, microvillus inclusion disease, HIV, Barth syndrome + cystic fibrosis and undefined patient.

**Conclusion:** IDI is a group disorder that difficult to manage for pediatric gastroenterologists. Genetic or molecular analysis is indicated in most cases for to confirm the diagnosis and it will reduce the invasive and unnecessary procedures Patients requires long-term TPN and hospitalization. Mortality rate seems to decrease in specialized centers in the near future.

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Objectives and Study: Congenital chloride diarrhea (CHD) is a rare disease presenting from birth with severe secretory diarrhea associated with electrolyte disorders and acid-base balance disturbance. Clinical presentation and biochemical changes in patients with CHD together with low awareness of paediatricians often course improper diagnostic approach with high-cost and invasive tests and delay the start of adequate salt substitution therapy increasing the risk of complications.

Method: We report 3 cases of congenital chloride diarrhea passed through our clinic between 2007-2017. In all children the final diagnosis was confirmed in our paediatric department with genetic testing found SLC23A3 mutations. Anamnesis, clinical manifestations and biochemical changes were summarized and preceding diagnostic mistakes were analyzed.

Results: All three children (2 girls and 1 boy) had similar antenatal anamnesis with polyhydramnios, dilated intestinal loops of the foetus, that led to suspicion of congenital intestinal malformation, and prematurity (31-34 weeks of gestation). All patients presented from birth with abdomen distension, «absence» of stool, abnormal weight loss. In all children typical clinical presentation in neonatal period led to repeated intestinal X-ray examination and laparoscopy in boy with the aim to exclude low intestinal obstruction. All children developed persistent profuse diarrhea despite of feeding practice accompanied with severe electrolyte changes beginning with hyponatraemia (&LT; 120 mmol/l) and hypochloraemia (&LT; 80 mmol/l) followed by hypokalaemia (&LT; 3,5 mmol/l) and metabolic alkalosis. Clinical presentation and electrolyte disorders demanded to exclude necrotizing enterocolitis, Hirschsprung’s disease, cystic fibrosis, adrenogenital syndrome, Bartter syndrome, Schwamman syndrome, congenital metabolic disorders. The first girl was diagnosed with CHD just at the age of 1 year with really late start of adequate salt replacement therapy and got complications of failure to thrive, psychomotor development delay, repeated hospitalizations in the first year of life for intravenous electrolyte infusions. The second girl was diagnosed at the age of 1.5 months, electrolyte and acide-base balance disorders were rapidly compensated with successful adaptation after hospital discharge and without need of following hospitalizations. No complications were observed. The boy was diagnosed at 7 months. The delay of constant salt replacement therapy led to the development of nephrocalcinosis.

Conclusion: Being a rare disorder congenital chloride diarrhea is an emergency in newborns that requires early diagnosis and adequate therapy. Both paediatricians and paediatric gastroenterologists should be aware of diagnostic criteria of congenital secretory diarrhea. Thorough analysis of antenatal anamnesis, clinical symptoms and laboratory data (electrolyte levels in blood and stool, acid-base balance) result in timely diagnosis and early start of substitution therapy preventing complications and improving patient’s quality of life as well as reduce costs in health care.

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Intestinal failure secondary to a disseminated Mycobacterium genavense infection in patient with a common variable immunodeficiency

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Objectives and Study: We present the case of a patient with intestinal failure secondary to a systemic Mycobacterium genavense infection. Accordingly, an in-depth immunological study was carried out which revealed the existence of a common variable immunodeficiency (CVID) due to a mutation in the NFκB1 gene (recently described as a cause of CVID).

Method: A retrospective case report.

Results: The patient, six years old at this time, was diagnosed with multisystem Langerhans cell histiocytosis at 6 months of age for which he received chemotherapy with corticosteroids, vinblastine and clorafarabine. At two and a half years of age he presents with prolonged fever accompanied by pancytopenia and progressive hepatosplenomegaly with digestive involvement in the form of malabsorptive diarrhea with failure to gain weight, along with pain and abdominal distention in connection with enteral nutrition requiring the start of parental nutrition. He is diagnosed with a disseminated Mycobacterium genavense infection, isolated using the PCR technique on biopsies of both the bone marrow and the small intestine, where a lack of a normal villous pattern can be observed and the presence of acid-fast bacilli within histiocytes in the lamina propria is noted. Four drugs are administered intravenously (IV) at standard doses: ethambutol, levofloxacin, rifampicin and clarithromycin. The diarrhea improves with the antibiotics but the pain and abdominal distention persist. Imaging tests (abdominal MRI and ultrasound) reveal mesenteric thickening with patchy contrast enhancement in line with mesenteritis. IV corticosteroid treatment is administered resulting in partial pain reduction. Nevertheless intestinal failure persists, requiring continued use of parental nutrition. An intestinal wall biopsy is performed revealing findings consistent with lymphocytic ganglionitis (predominately T, CD3+) in the muscularis propria. After nearly two years of IV antibiotic treatment the intestinal mucosa biopsy results come back normal but malabsorption and dysmotility persist. Currently, the patient receives parental nutrition 5 days per week and we were able to progressively reduce the dose of corticosteroids to the point of stopping their administration completely three years after the start. During this time period the patient was diagnosed with a CVID, secondary to a mutation of NF-κB1.

Conclusion: Our patient developed a condition of permanent intestinal failure rendering him dependent on parental nutrition due to a disseminated Mycobacterium genavense infection in the context of a CVID previously undiagnosed. Although pain episodes were reduced with corticosteroids and intestinal mucosa lesions successfully resolved with antibiotics, the patient is still affected by malabsorption and significant dysmotility, with histopathological findings consistent with a gastrointestinal neuromuscular disorder.

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A two-and-a-half-year-old boy with lymphocytic colitis, presented with chronic intractable watery diarrhea

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**Introduction:** Microscopic colitis (MC) is a chronic inflammatory disease presented with chronic watery diarrhea, weight loss, and abdominal pain. There are two subtypes, lymphocytic colitis and collagenous colitis, which are similar with regards to clinical manifestations and epidemiology. MC is usually found in older age (more than 60 years), and female gender. Herein we report a toddler boy with a presumed diagnosis of MC.

**Case:** A 2.5 year-old-Thai boy had chronic diarrhea for one year without abdominal pain, nausea, vomiting, or bloody stool. The weight and height was in the 10th percentile, other examinations were unremarkable. The investigations revealed hypokalemia with metabolic acidosis with normal erythrocyte sedimentation rate, C-reactive protein, and serum albumin level. Stool examination showed *Trichomonas hominis* trophozoite without white blood cells, red blood cells, or fat globules. After a trial of metronidazole, the trophozoite was not found. However, the patient came back due to severe diarrhea and electrolyte imbalance. Upper endoscopy and colonoscopy showed normal appearing mucosa. Histopathology demonstrated increased intraepithelial lymphocytes of the ascending, transverse and descending colonic mucosa without tissue eosinophilia, cryptitis, crypt architectural irregularity or crypt abscess. Gastric and duodenal mucosa were normal. The immunologic function tests, specific IgE for cow's milk, soy, wheat and mixed seafood and serum tissue-transglutaminase IgA were normal. He was treated with several therapeutic trials including cholestyramine, loperamide, intravenous octreotide, sulfasalazine, cow's milk protein and gluten elimination, but the diarrheal symptom was not improved. We decided to try oral prednisolone for one week which led to significant improvement of clinical symptom and electrolyte imbalance. Therefore, we presumed a diagnosis of lymphocytic colitis in this patient.

**Conclusion:** Lymphocytic colitis can present at a very young age with chronic intractable watery diarrhea, normal endoscopic finding with increased intraepithelial lymphocytes in the colon. Oral prednisolone may be useful in improving the patient's clinical symptom.

**Key word:** Chronic diarrhea; lymphocytic colitis; microscopic colitis.

**Reference:**

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Bifidobacterium spp. try to modulate Microbiota of infants: a new approach to food allergy?

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Objectives and Study: The gut microbiota plays a pivotal role in immune system development and function. Modification in the gut microbiota composition in early life is a critical factor affecting the development of food allergy. Many environmental factors including caesarean delivery, lack of breast milk, drugs, antiseptic agents, and a low-fiber/high-fat diet can induce gut microbiota dysbiosis, and have been associated with the occurrence of food allergy. New technologies and experimental tools have provided information regarding the importance of select bacteria on immune tolerance mechanisms. The probiotic's ability to modulate the intestinal microbiota is controversial.

Method: Infants aged 10-14 months, allergic to egg/milk (group I) received Tribif (Bifidobacterium longum [BL], B. breve [BB] and B. infantis [BI] for 30 days. Fecal samples at 0, 7, 15, 30, 60 and 90 days were evaluated by specific BL, BB and BI primers and probes. Two control groups of egg/milk IgE-positive infants with negative food challenge (group II) and IgE-negative healthy infants (group III) were evaluated for BL, BB and BI in basal conditions.

Results: Of 35 infants (mean age 13.28±2.13 months), 12 (group I) were challenge-positive to egg or milk. Group II was composed by 11 infants, group III by 12. BL harbours the microflora of all children irrespective of their atopic status; BB was absent in 5/25, all in group I. The concentration increase of BL and BB was observed in 7/10 patients analyzed at different times points compared to baseline due to the assumption of the probiotic from time T1. On the contrary, BI concentration increased at different times points from baseline in 10/10 patients, while in 8/10 patients the strain concentration was 0 at baseline.

Conclusion: BL and BB are part of the normal bacterial microflora. A significant increase in BL and BB concentration suggests that Tribif® does colonize the intestinal tract. On the other side, the BI seems not to be part of the gut microbiota and its concentration increased after probiotic intake. When the baseline concentration is low the Tribif® administration may be restores the ecological niche of bifidobacteria when it is depleted.

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Omalizumab with severe food allergy: perhaps more than a simple good idea

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Objectives and Study: Therapies for food allergy include elimination diets, Oral ImmunoTherapy (OIT), and the administration of biologics. Despite a growing awareness of food allergy, adherence to avoidance diets is very difficult, quality of life is markedly affected, and accidental ingestions remain common. It is known that Omalizumab may increase of about 80% the peanut tolerated dose among peanut-allergic patients. In Europe, Omalizumab has been licensed for use in severe allergic asthma and chronic urticaria. We aimed to evaluate the effect of Omalizumab on various food allergy in children with severe asthma.

Method: Children with severe asthma (GINA guidelines) and anaphylactic reactions to foods treated with Omalizumab as add-on asthma therapy were retrospectively evaluated. All patients were in inadequate asthma control (ACT ≤ 19) despite treatment with high dose inhaled corticosteroids (250 mcg/day FTC for children < 12 years, 500 mcg/day for older patients) and another medication. All were sensitized to perennial aeroallergens, had a baseline IgE between 30 and 1500 IU/ml in at least two consecutive determinations. Food allergy was confirmed and the threshold dose for each food established by a double-blind, placebo-controlled oral food challenge (DBPCFC) at screening. The patients underwent a further DBPCFC within two to four weeks after the fourth dose.

Results: We enrolled 15 patients (12 Males, median age 11.5, range 7-20.75 years). The mean serum total IgE value was 672.67 kU/L, and their asthma was out of control despite treatment as per GINA III or IV step. The foods involved were milk (13 children, 7 of whom reactive to baked milk), egg (8 children, one reactive to baked egg), wheat (3 cases), and hazelnut (2 cases). After treatment, 8/15 patients showed full tolerance to all food they were allergic to. The other 7 patients showed an important increase of the tolerated dose of food: 303 times for cow milk, 155 times for egg, 13 times for wheat and 24 times for hazelnut at DBPCFC.

Conclusion: In addition to avoidance and oral immunotherapy (OIT), the administration of Omalizumab can clinically reduce food allergy. This treatment can be used as an adjunct to OIT or as a substitute, as a gradual increase in food dose is not necessary in the majority of cases. Pharmacoeconomics considerations may limit the use of this treatment in children who have food anaphylaxis, but not asthma.

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Two cases of Microvillous Inclusion Disease (MVID) in Siblings with Novel MYOB5 gene mutation

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Objectives and Study: We describe two clinical cases of Russian siblings with MVID and novel mutation in MYOB5 gene

Method: A molecular genetic analysis was carried out in two siblings. Sequencing of the clinical exom using the Ion C5 sequencer (Thermo Fisher Scientific) was performed in the 1st sibling. Clinically significant genomic variants were checked using the database of human mutations HGMD Professional. The analysis of previously undescribed mutations was done by the computer program Alamut Visual (Interactive Biosoftware), which allowed to determine the functional significance of mutations using built-in modules SIFT, PolyPhen and Mutation Taster. After analyzing the results, exons 11 and 16 of the MYO5B gene with adjacent intron regions investigated by direct automatic sequencing in the second child

Results: Patient 1, a girl born from the 1st pregnancy in non-consanguineous marriage from healthy parents of Russian nationality. Ultrasound revealed polyhydramnios and dilation of fetal intestinal loops prenatally. Birth weight 4000 g. On the 7th day of life she was transferred to ICU with weight loss, diarrhea, vomiting, intestinal paresis. In the first 2 weeks of life, she was fed with expressed breast milk, protein hydrolysate formula, then total parenteral nutrition, however, diarrhea and vomiting persisted. She entered our hospital at the age of 3 months with dystrophy, malabsorption, acidosis, electrolyte disturbances, bacteremia. On gastroscopy atrophy of the villous layer, flattening and scalloping of intestinal folds; on microscopy villous atrophy, deep crypts, fragmented brush border, with PAS- and immunohistochemical reaction with CD 10 the areas of its agglomeration, absence, fragmentation, and decay were seen. Electron microscopic examination confirmed the presence of microvilli inclusions. Central long-standing catheter was implanted, we managed to cope with infectious and metabolic complications and get weight gain. She was discharged for home parenteral nutrition, but unfortunately died after 2 months due to upper vena cava thrombosis, catheter sepsis. Her brother (patient 2) was born shortly before the death of his sister in the same marriage; with intranatal asphyxia, respiratory failure; weight loss, bloating, diarrhea, acidosis, electrolyte disorders, anemia, thrombocytopenia; bilateral polysegmental pneumonia; villous atrophy in the jejunal biopsy. Despite intensive therapy in ICU, he died on the 29th day of life because of sepsis, multiple organ failure. The characteristic microvillous inclusions in the apical parts of enterocytes were found post mortem. Both infants had two identical MYO5B variants - the previously undescribed heterozygous nucleotide substitution c.1404+1G>T related to the 1st class of pathogenicity and heterozygous missense mutation c.1966C>T described previously in patients with MVID. The molecular-genetic analysis of the parents revealed the carriage of variant c.1404+1G>T in mother and the mutation of c.1966C>T in father

Conclusion: We describe two clinical cases of MVID in Russian siblings caused by compound heterozygous mutations in MYO5B gene. Nucleotide substitution c.1404+1G>T, which can lead to the creation of a new splice site was first discovered and not described in the international mutation databases previously

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Food Protein Induced Enterocolitis Syndrome and Down Syndrome: could it be possible?

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Objectives and Study: Food Protein Enterocolitis Syndrome (FPIES) is a non-IgE food allergy with an unknown prevalence and pathophysiology. Acute FPIES manifests within 1-4 hours after ingestion of incriminated food with repetitive emesis, pallor, lethargy, and water or bloody diarrhea progressing to dehydration and a possible hypovolemic shock. Gastrointestinal (GI) disorders in Down Syndrome (DS) are predominantly related to anatomical anomalies in about 6.7% of DS patients: esophageal atresia/tracheoesophageal fistula, pyloric stenosis, duodenal stenosis/ataresia, Hirschsprung disease and anal stenosis/ataresia. Furthermore, DS is associated with increased risk for coeliac disease (CD), an immune-mediated gastrointestinal disorder characterized by inflammation of the small intestine on exposure to gluten, a protein found in wheat, barley, and rye.

The first cases of NON-IgE mediated food allergy in DS were described in a letter to the editor in 2015. In these cases the patients showed severe and longlasting symptoms and authors speculate that it could be due to the described impaired IL-10 production in DS. Nevertheless a possible association between DS and food allergy it was never supposed.

Method: A retrospective descriptive single-center study was conducted. Subjects included in this study were children with acute FPIES who entered in our institutional follow-up protocol between January 2013 and June 2017.

Results: Among the 51 patients (thirty-one boys), eight (15.7%) were affected by DS. In our population, the FPIES triggers included different foods (such as milk, egg, fruit, fish, wheat, etc.). Seven patients with a Down phenotype showed FPIES reactions after the ingestion of cow's milk and one of them even with beef meet, while the remaining eighth with fish. Patients with Down syndrome experienced acute FPIES reactions with a severity degree comparable to that reported in other patients, ranging from mild-moderate (repetitive vomiting with less than three episodes of emesis and pallor) to severe (repetitive vomiting with more than three episodes of emesis, pallor, lethargy, dehydration) or very severe (severe symptoms plus cyanotic appearance and water/bloody diarrhea).

Conclusion: We believe that this type of manifestation may soon be considered another frequent pathology in patients with DS.

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Necrotizing enterocolitis and cow's milk proteins allergy: a possible causative association

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Introduction: Necrotizing enterocolitis (NEC) is the more frequent gastrointestinal disease in newborn. The aetiology of NEC is not yet completely clear but a role of cow's milk allergy has been hypothesized.

Methods: A retrospective study divided into two parts has been designed. Part A consists on data collection on all children which have undergone allergic tests during 24 months following a discharge from neonatology for gastrointestinal disease. Part B is a study of NEC risk factors on children with small bowel syndrome due to extensive bowel resection for NEC who required long term parenteral nutrition.

Results: In part A we enrolled 34 children with a history of either NEC (10), other digestive surgery (12), or rectal bleeding (12). Among them, cow's milk IgE positivity (5) was found only in children after NEC. Patch tests positivity did not showed any significant association. Furthermore a significant association was found between positive allergic tests and small bowel resection. For part B we enrolled 35 children. By analysing NEC risk factors for all patients we found that 3 of them did not present any recognized risk factor. For the three of them allergic testing was done and cow's milk IgE were found positive in all of them. A reintroduction of cow's milk protein was possible only in 1 of them after 18 months of life.

Conclusion: Cow's milk allergy seem to have a role in the development of severe NEC that can lead to various degree of small bowel resection.
A novel mutation in the EPCAM gene in a patient with Congenital Tufting Enteropathy without typical electron microscopy findings

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Objectives and Study: Congenital diarrheal disorders are a group of rare inherited intestinal disorders characterized by persistent life threatening intractable diarrhea and nutrient malabsorption, emerging during the first weeks of life, often fatal. The diagnosis is difficult and most of the times requires biopsies. The aetiology is diverse, but several are associated with defects in the enterocytes, that include microvillus inclusion disease and congenital tufting enteropathy (CTE) among others. Mutations in the epithelial cellular adhesion molecule EPCAM gene were identified as causative for CTE.

We report on a case of an infant with CTE who presented with severe diarrhea and failure to thrive that despite multiple interventions ended passing away. This report illustrates that CTE may be missed by endoscopic and anatomopathological studies, and the use of molecular analysis like whole exome sequencing may be crucial to clarify the diagnosis when biopsies and electron microscopy are inconclusive.

Method: The proband is a 4 month old female, that from the first day of life presented with profuse acuuous diarrhea, accompanied by recurrent infections, metabolic acidosis with severe dehydration, anemia, growth retardation and postnatal microcephaly. No resolution of symptoms were observed with change of formula. Endoscopic studies were made and biopsies for electron microscopy were taken. Whole exome secuency was performed.

Results: The endoscopic studies evidenced villous atrophy of the bulb and second duodenal portion. At colon there was no mucosal lesion. The electron microscopy showed no abnormality in villous structure and no tuft cells were observed. Whole exome sequencing showed a compound heterozygous novel mutation in EPCAM gene (exon 1-3 del; c.492-3C>G).

Conclusions: Pathogenic mutations in EPCAM are associated with congenital tufting enteropathy. In cases of patients with congenital diarrhea who presents with villous atrophy in endoscopy but inconclusive electron microscopy, whole exome sequencing is an effective analysis identifying pathogenic mutations associated with this disorder.

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Extra-intestinal manifestations of children with genetically confirmed microvillus inclusion disease

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Objectives and Study: Microvillus inclusion disease (MVID) is a congenital disorder caused by MYO5B or STX3 gene mutations. Pathognomonic features are severe intractable diarrhoea and malabsorption due to intestinal brush border atrophy with accumulation of lysosomal granules and microvillus inclusions in the apical cytoplasm of enterocytes. MYO5B is expressed in all epithelial tissues and it is currently unclear if organs other than the gut are affected. However, isolated case reports of renal or primary hepatic involvement are described in the literature.

Method: We present two male children: Patient A, 2 year old of Pakistani origin and patient B, 12 month old from Kuwait; with confirmed MYO5B mutations.

Results: Patient A presented with severe secretory diarrhoea from birth. He had high fluid and electrolyte requirements and became severely unwell when feeds were introduced. Duodenal histology showed blunted villi with hyperplastic crypts, loss of surface epithelium, goblet cell depletion and apoptosis. Periodic acid-Schiff (PAS) and CD10 staining suggested MVID, confirmed by electron microscopy (EM). Genetic testing of the MYO5B gene revealed homozygosity for c.1087C>T mutation. He was stabilized on parenteral nutrition (PN) and discharged on home PN after 10 months. He continued to have high volume and sodium requirements with gradually worsening diarrhoea. He developed minor transaminitis in the first year of life but otherwise stable liver function. On routine annual PN screening, he was found to have low TMP/GFR (0.89mmol/L), elevated cystatin C (1.27mg/L), biochemical evidence of renal tubular leak, radiological signs of rickets but no radiological evidence of nephrocalcinosis. Fanconi syndrome was diagnosed. An inter-current illness markedly increased his fluid and electrolytes requirements requiring major adjustments to his PN regime. He no longer tolerates time off PN, requires 250ml/kg of fluid, large amounts of electrolytes, phosphate and acetate and has over 20 watery stools daily. He was referred for small bowel and possible renal transplant. Patient B presented as a neonate with watery diarrhoea and severe acidosis when feeds were introduced. He was commenced on PN and referred to a tertiary centre in London at the age of 2 months where he arrived in poor nutritional status with marked jaundice, conjugated hyperbilirubinemia and transaminitis. His small bowel mucosal biopsies demonstrated total villous atrophy with focally vacuolated superficial epithelium and few intraepithelial lymphocytes. PAS and CD10 staining suggested microvillus inclusions confirmed by EM. On genetic testing he was compound heterozygous for MYO5B gene mutations; c.1576C>T; p. and c.2111del; p. variant. Liver biopsy revealed severe changes of lobular cholestasis with hepatocyte giant cell transformation and bridging fibrosis. He currently tolerates a small amount of an amino acid based formula and 170ml/kg PN daily with a 10 hour break. His diarrhoea is stable with 6 to 7 watery stools per day. In view of his severe liver injury and long term PN, he is being assessed for combined liver and small bowel transplant.

Conclusion: MVID appears to have a variable phenotype. The severity of diarrhoea differs significantly between patients and other organs such as the liver and kidney can be affected.

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A prospective study on the clinical profile of Cow’s milk protein allergy in children as seen in a tertiary referral centre

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Objectives and Study: To find out in Cow’s milk protein allergy (CMPA)
- Clinical symptoms/signs
- Outcomes of therapeutic intervention
- Association of Soya protein allergy

Method: Prospective observational study.

Inclusion criteria
- Children aged more than 1 month & less than 60 months, with symptoms/signs of CMPA & improvement on cow's milk protein (CMP) elimination diet as per ESPGHAN guidelines.

Exclusion criteria
1. Children with underlying chronic disease
2. Multiple food allergies

Fifty-six (56) were eligible for study. In 2 children carers did not consent and 4 lost to follow up. Hence fifty (50) children formed the study cohort. All were commenced on CMP elimination diet and followed up every fortnight for 6 weeks. All except those with severe symptoms, who improved with CMP elimination diet, were challenged with CMP to look for recurrence of symptoms, thus confirming CMPA diagnosis.

Results: CMPA was common among children less than 2 years (56%). More than half (68%) were boys & 42% had a positive family history of atopy. Presenting Symptoms usually involved at least one more system apart from gastrointestinal system. Diarrhoea & blood in stools was the most common (52%) GI symptom. Cough was the most common respiratory symptom followed by allergic rhinitis, wheeze & fast breathing. Atopic eczema was the most common cutaneous manifestation.

IgE mediated CMPA was seen in 34% of our cohort. In this subgroup significant GI symptoms included regurgitation, vomiting & blood in stools and allergic rhinitis was the significant respiratory symptom.

There was a significant association between IgE mediated CMPA & IgE mediated soy allergy. In Non IgE cohort (66%) the significant GI symptom was constipation (55%) & predominant respiratory symptom was wheezing (table 1). Soy milk non-responders were noticed to be significant in Non-IgE CMPA. In our entire cohort, Soy allergy was noticed in 26% of CMPA & all these children improved well on extensively hydrolysed formula (EHF).

<table>
<thead>
<tr>
<th>Factors</th>
<th>IgE Mediated CMPA (n=17) Number (Percentage)</th>
<th>Non IgE Mediated CMPA (n = 33) Number (Percentage)</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitation</td>
<td>15 (88)</td>
<td>7 (21)</td>
<td>22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (94)</td>
<td>9 (27)</td>
<td>25</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Blood in stools</td>
<td>15 (88)</td>
<td>18 (54)</td>
<td>33</td>
<td>0.004*</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>14 (82)</td>
<td>4 (12)</td>
<td>28</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (12)</td>
<td>18 (54)</td>
<td>20</td>
<td>0.001*</td>
</tr>
<tr>
<td>IgE soya postive</td>
<td>4 (24)</td>
<td>2 (6)</td>
<td>6</td>
<td>0.001*</td>
</tr>
<tr>
<td>Chronic duodenitis</td>
<td>4 (24)</td>
<td>1 (3)</td>
<td>5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Focal eosinophilia</td>
<td>8 (47)</td>
<td>4 (12)</td>
<td>12</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

[Significant characteristics in CMPA children]
Our first step in therapeutic intervention for infants less than 6 months, was continuation of breast-feed with maternal exclusion of CMP in those who were exclusively breast fed and EHF in formula fed infants. In children aged more than 6 months, soy based formula/milk was our first step, second step was EHF and third step was amino acid formula (AAF). Effectiveness of intervention - CMP exclusion in mother, Soy milk, EHF and AAF was 60%, 80.5%, 85.5% and 100% respectively.

**Conclusion:** This study highlights the challenges in diagnosis of CMPA in Indian subcontinent where data is scarce. A diagnosis of CMPA needs to be considered in children with persistent regurgitation/vomiting and in those with chronic constipation (Non IgE mediated) who are not responding well to optimal medical management. Diagnosis need to be confirmed with CMP re-challenge. It is advisable to check serum specific IgE to soya milk in CMPA as there is coexistence of soy allergy in 26%.

In our setup we would recommend soy formula/milk as a first line therapeutic intervention for children more than 6 months of age with CMPA. If IgE to Soy milk is significantly positive or when there are severe symptoms, we suggest commencing these children on CMP & soy free formula/diet, which would be EHF initially and then AAF if no improvement to EHF.

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TH1 and TH17 cytokines are elevated in the rectum in children with non IgE mediated cows milk protein allergy

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**Objectives and Study:** Cow’s milk proteins allergy (CMPA) has a prevalence ranging from 2.2% to 2.8% and is the result of an alteration in the intestinal immunity, therefore probably an imbalance in the differentiation of T cell naive in TH1 and TH2. The clinical picture is broad and includes various organs (gastrointestinal tract, skin and respiratory system). So far there are few studies that have evaluated all cytokines involved in the Treg and TH1 response. Also in the previous studies have not been evaluated cytokines at rectum, a place that certainly is affected, this is inferred by the previous study in our hospital where there were up to 87% of infiltration of eosinophils in children with CMPA. In the case of non-IgE-mediated CMPA are lack of understanding of the pathophysiology of the disease.

**Objective:** The aim of this study was to evaluate differential cytokine gene expression of Tres, TH1, TH2 and TH17 in the mucosa of rectum and dodenum in patients with cow’s milk protein allergy.

**Method:** Observational, descriptive, cross-sectional, prospective study; In children with suspected CMPA open challenge were performed, if it were positive, specific IgE (ImmunoCAP) and endoscopy and rectosigmoidoscopy be held, with biopsy in rectum and duodenum. All mucosal biopsies taken from endoscopy were immediately placed in RNA later and stored at -70 °C until processing. Then total RNA was isolated using High Pure RNA Tissue. Two hundred nanograms of total RNA was reverse-transcribed into cDNA with random hexamer primers. The gene expression of IL-6, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-17 and TNF were measured by real-time polymerase chain reaction (RT-PCR). Expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a housekeeping gene was analyzed for normalization purposes and quality controls. Statistical analysis was performed using the SPSS 17 program Descriptive statistics for frequencies, means and standard deviations also U-Man Whitney test were performed for comparasion of cytokines expressed. A p value ≤ 0.05 was considered as significant.

**Results:** 30 patients were included in the study, the mean age were 4.03 months (±5.28), 13 boys and 17 girls. The principal histopathological finding in duodenum were normal, and in rectum were nodular lymphoid hyperplasia and proctitis. The gene expression of inflammatory cytokines: IL-6, IL-13, IL-17 and TNF were higher in rectal mucosa biopsies compared with duodenum (p=0.034, p=0.043, p=0.045, p= 0.037). See Figure 1.
Conclusion: TH1 and TH17 are expressed higher in rectum in children with non IgE mediated CMPA. Much remains to be learned about the pathogenic mechanisms that lead to CMPA. This cytokine profiles imbalance may be implicated in the pathogenesis of milk allergy.

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GASTROENTEROLOGY - Enteropathy (other than Coeliac disease)

G-P-137

Clinical features and next-generation sequencing in children with early-onset protein-losing enteropathy

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Objectives and Study: We examined the phenotypes and performed next-generation sequencing in children with early-onset protein-losing enteropathy.

Method: We enrolled 27 children with early-onset protein-losing enteropathy. Patients were characterized on clinical, immunologic and systemic involvements. Targeted panel sequencing and whole exome sequencing were performed. This study was approved by the Ethical Committee of Children's Hospital, Fudan University.

Results: In all, 27 patients [55.6% male] were identified. Median age of onset among patients was 173 days postnatal. Most had initial gastrointestinal symptoms, and all had hypoalbuminemia. Upper endoscopy showed typical presentation of intestinal lymphangiectasia (n=13). Next-generation sequencing among 9 patients with available DNA showed one patient had CCBE1 mutations and two had novel homozygous DAGT1 mutations. Patients partially responded to albumin, immunoglobulin transfusion and parenteral nutrition. Overall mortality was 12.5% among patients.

Conclusion: Early-onset protein-losing enteropathy can be associated with multiple system involvements. Genetic etiology should be considered, and monogenic diseases might be common among these patients.
[Fig. 1A Upper endoscopy. Fig. 1B Abdominal CT.]

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Atypical late-onset IPEX syndrome with intractable diarrhea: a case report

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Objectives and Study: The aim of the study is to present one case of atypical late-onset Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome with intractable diarrhea.

Method: Clinical manifestations of a 6 year and 9-month-old boy with a history of 6-month intractable diarrhea were retrospective summarized. Deep sequencing was used for Forkhead Box Protein 3 (FXOP3) gene mutation identification.

Results: The boy had intractable diarrhea, abdominal pain, recurrent infections, and failure to thrive. The patient was received metronidazole, teicoplanin, fluconazole, mycamine, ceftriaxone, azithromycin and fecal microbiota transplantation (FMT) for treating infections, methylprednisolone and infliximab for suspicion of Crohn's disease (CD). However, the clinical manifestations of the patient were not improved. Finally, the boy was diagnosed as IPEX syndrome due to a c.1190G>A (p. R397Q) mutation in exon 11 of the FOXP3 gene. At 3 months after the genetic diagnosis of IPEX, at age of 7.5 years, the boy underwent matched sibling peripheral blood hematopoietic stem cell transplantation (HSCT).

Conclusion: Our findings suggests that IPEX should be considered in cases of late-onset, mild forms, and less typical clinical manifestations to avoid diagnostic delay.

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D-lactic acidosis in children with Short Bowel Syndrome: comparison between children who underwent or not lengthening surgery

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Objectives and Study: D-lactic acidosis (DLA) is a relatively frequent complication in children with Short Bowel Syndrome (SBS) whose the remnant bowel is affected by extensively dilated. This condition is related to an excess D-lactate production by intestinal bacteria when carbohydrates (CHO) are not completely absorbed in the small bowel. Our aim was to evaluate the incidence of DLA in SBS children who underwent autologous gastrointestinal reconstruction procedures (AGIR) compared with SBS children treated with non-surgical reconstruction.

Method: We performed a 10-year retrospective analysis of SBS patients referred to Royal Manchester Children's Hospital (UK) and AOU Federico II of Naples (Italy) respectively investigating demographic data, bowel length, antibiotic treatment, and CHO intake. Data are expressed as means±SD. Incidence of DLA episodes was expressed per 100 patient days.

Results: Forty-three patients with SBS were enrolled (25 M, 58%), 23 underwent AGIR and 20 did not undergo surgery, with a median age at time of follow-up of 82 ±26.6 months and 71.5±76.7 months, respectively. Age at time of surgery was 13.7±16.7 months and 9.8±35.7 months respectively. The underlying diagnoses responsible for SBS were enterocolitis necrotising (25%), complicated gastroschisis (25%), volvulus/malrotation (21%), small bowel atresia (19%), Hirschprung disease (7%), diaphragmatic hernia (3%). Eleven out of 20 (55%) patients without surgical reconstruction developed at least an episode of DLA during the follow-up, compared with 8/23 (34%) who underwent AGIR (p=0.18). The mean number of DLA episodes/child was higher in children who did not undergo AGIR if compared with those undergoing AGIR, although this difference does not reach statistical significance (3.56±6.5 vs 0.91±1.8, p= 0.11). This trend was still persistent after normalizing the number of episodes for 100 at-risk patient days (2.89±4.4 vs 1.5±3.1/100 days, p=0.24).

Children presenting DLA had a bowel length shorter than those without episodes of DLA (38.21 vs 51.1±36 cm, p=0.18).

No correlation was observed between underlying diseases, presence of colon or ileocecal valve, age of the patients at the time of surgery, way of weaning or feeding and development of DLA. Neurological symptoms or behavioural changes were the symptoms reported. All children were eventually allowed access to free diet. The treatment of DLA was similar in both centres and consisted in 24h of starvation with only oral/IV fluid intake, slow re-introduction of CHO and change of antibiotics.

Conclusion: DLA is a rare but potentially serious complication of SBS, which should be suspected in the presence of neurological symptoms and behavioural changes. Our results show that there is a reduction of DLA incidence in children who underwent AGIR surgery respect to children treated without lengthening surgery.

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Association between exposure to macrolides and the development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis

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Objectives and Study: Macrolides are bacteriostatic antibiotics with a broad spectrum of activity against Gram-positive bacteria. The aim of this study was to systematically review and meta-analyze the association between infantile hypertrophic pyloric stenosis (IHPS) and macrolides.

Method: Nine databases were searched systematically for studies with information on the association between macrolides and IHPS. We combined findings using fixed- and random-effects models.

Results: Our study revealed 18 articles investigating the association between macrolides and IHPS. There was a significant association between the development of IHPS and erythromycin (2.38, 1.06 - 5.39). The association was strong when erythromycin was used during the first two weeks of life (8.14, 4.29 - 15.45). During breastfeeding, use of macrolides showed no significant association with IHPS in infants (0.96, 0.61 - 1.53). IHPS was not associated with erythromycin (1.11, 0.9 - 1.36) nor macrolides use during pregnancy (1.15, 0.98 - 1.36).

Conclusion: There is an association between erythromycin use during infancy and developing IHPS in infants. However, no significant association was found between macrolides use during pregnancy or breastfeeding. Future larger prospective studies are necessary to evaluate this association.

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Comparative analysis of PEG +E with stimulant laxative versus PEG+E alone for disimpaction regimen - a study from a tertiary centre in Eastern India

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Objectives and Study: Chronic constipation is not uncommon in Asian countries though it was previously thought so. Oral Polyethylene Glycol 3350 and electrolytes (PEG+E) is accepted as the best available method for faecal disimpaction. But PEG+E alone was not producing the desired results in all patients. Addition of a stimulant laxative along with the PEG +E was achieving a faster and better result in terms of disimpaction. So this randomized study was conducted to compare the efficacy of both the regimen.

Methods: This prospective study had been carried out in a tertiary centre in Kolkata, India from May 2015 to Dec 2016. All children( aged 2-14 years) were suffering from functional constipation (diagnosed by ROMEIII criteria. These children were randomized to have PEG+E with stimulant laxative (Sodium Picosulfate) or PEG +E solution alone for disimpaction regimen. All of the children were hospitalized for 2 days to receive the treatment and observe closely. Faecal impaction was decided on abdominal examination where a fecal mass were palpable or in abdominal X ray (done in 15% who came with severe abdominal pain). All were given a domperidone (dose 0.25mg/kg) at the onset. 30 minutes after PEG + E was given at 3 gram /kg body weight of PEG dissolved in drinking water or juice to drink over 2 - 3 hours. In the stimulant group Sodium Picosulfate syrup was given at 1mg/kg in two divided doses at 8 hours interval. The same regimen was repeated on the 2nd day. 9 parameters (Table1) were selected to assess the efficacy of each regimen. All children were followed up after 1 week and then every 2 months for at least 1 year

Results: Total of 101 children participated and completed follow-up. 50 received PEG+E and 51 received PEG+E and Sodium Picosulphate. Age range was same from 2 - 14 years in both the groups with mean age of 6.5 years. Girls were more (61) than boys (50).
<table>
<thead>
<tr>
<th>Efficacy parameters</th>
<th>PEG+E (n=50)</th>
<th>PEG +E &amp; Picosulfate (n=51)</th>
<th>p value (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of stools achieved on the 1st day.</td>
<td>2.5 (0.92)</td>
<td>5 (1.02)</td>
<td>&lt;.0001 (2.12 to 2.88)</td>
</tr>
<tr>
<td>No of stools achieved on the 2nd day</td>
<td>5 (1.02)</td>
<td>7(1.12)</td>
<td>&lt;0.0001 (1.57 to 2.42)</td>
</tr>
<tr>
<td>Nausea/vomiting during taking medication</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal distension and pain (no of children)</td>
<td>15(1.2)</td>
<td>3(1.03)</td>
<td>&lt;.0001 (-12.44 to -11.55)</td>
</tr>
<tr>
<td>Reduction of perianal pain during defecation (2nd day)</td>
<td>40</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>average stool frequency achieved on 1st week</td>
<td>Once/2days 3.5/wk(0.84)</td>
<td>Once/day 7/wk(1.2)</td>
<td>&lt;.0001 (3.09 to 3.9)</td>
</tr>
<tr>
<td>average stool frequency achieved on 2nd week</td>
<td>Once/day 7/wk(1.5)</td>
<td>Twice/day 14/wk (2.1)</td>
<td>&lt;.0001 (6.27 to 7.72)</td>
</tr>
<tr>
<td>Stoppage of incontinence (mean time)</td>
<td>30 days(5.4)</td>
<td>16 days (4.6)</td>
<td>&lt;.0001 (-15.97 to -12.02)</td>
</tr>
<tr>
<td>Global satisfaction of parentsψ</td>
<td>3(1.2)</td>
<td>3(0.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

[Efficacy outcomes]

Ψ 5- very happy; 4- happy ; 3-satisfactory; 2 less satisfactory; 1- no satisfaction NS: not significant

Total duration of constipation treatment was 1 year in all patients from where doses were tapered gradually as per individual tolerance.

**Conclusion:** Faecal disimpaction is achieved well using a 2 day PEG +E regimen with a good compliance and efficacy. Addition of a stimulant laxative with PEG achieves bowel clearance safely and significantly more efficiently laying a good foundation for the long term outcome of the management of functional constipation. To the best of our knowledge this is the 1st study of its kind to combine stimulant and PEG for disimpaction.

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Probiotic or zinc, which is more effective in treatment of diarrhea in children?

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Objectives and Study: Diarrhea leads to 5-10 million deaths in the age group of 0-4 years old per year, especially in Asia, Africa, and Latin America. Zinc is one of the essential micronutrients that thought to play a key role in improving or preventing diarrhea. Additionally, it is shown that the use of probiotics are useful in the prevention and control of gastrointestinal diseases, particularly diarrhea resulting from prolonged use of antibiotics. Therefore, the aim of this study was to determine and compare the effects of probiotics and zinc supplements on the mean duration and frequency of acute diarrhea in children aged 6 months to 2 years.

Method: This was an interventional or clinical trial study in which the data of all healthy infants (6 months to 2 years old) who were admitted for moderate to severe diarrhea to Shahid Madani Hospital of Khorramabad were collected through a questionnaire. After selecting the patients according to the criteria of entry (eligibility criteria or inclusion criteria), the patients were divided into two groups called Zinc Receiving Group (ZRG) and Probiotic Receiving Group (PRG), using randomized block allocation method. The two groups were checked according to the frequency of diarrhea in the first 24 hours and 48-72 hours, the duration of hospitalization and the duration of diarrhea persistence for 3 and 7 days. In the case of discharge of these children from the hospital, information about the persistence of diarrhea was obtained by calling the parents. Patients’ follow up were done in terms of the outcomes mentioned by someone other than the researchers (trained nurse) and were equally applied into two groups. The primary sampling method for children was according to age range and the criteria for entering to the study.

Results: According to our findings regarding the comparison of the improvement of diarrhea in patients treated with probiotic and zinc, it was found that, diarrhea was continued up to the third day of admission in 100% of PRG, while only in 76.1% of ZRG children, diarrhea continued until the third day of admission, and this difference was statistically significant based on Fisher’s exact test. Further, the relative risk of diarrhea persistence in the PRG, was 1.31 times more than ZRG until the third day. Also, 80% of diarrhea cases in the PRG persisted until the fourth day of admission, while it was shown only in 47.8% of the ZRG, and this difference was statistically significant based on the Chi-square test. The relative incidence of diarrhea persistence was 36.4 times more than the ZRG in the PRG up to the fourth day. Also, the percentage of complications after treatment was 35.5% in the PRG and 2.6% in the ZRG, which was statistically significant. However, there was no significant difference in the distribution of frequency of children’s weight, bowel habits, sex, residence, mother’s education level or the type of nutrition of infants in the two groups on the basis of independent t-test.

Conclusion: In our study, Zinc’s effectiveness in treatment of diarrhea at a dose of 20 mg was higher than probiotics. Also, the complications of zinc supplements were lower than probiotics.

Keywords: Diarrhea, Probiotics, Zinc, pediatrics

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Background: Obscure gastrointestinal (GI) bleeding is a challenging condition for diagnosis and treatment. Thalidomide was used in adults to treat GI bleeding from vascular malformation, but has never been reported to treat GI bleeding in children. It has been used in children safely for other indications like inflammatory bowel disease. We report a successful use of thalidomide to stop obscure GI bleeding in a child.

Case report: A 6-year old girl underwent liver transplantation for end stage liver disease due to choledochal cysts at age 3 years. She presented with iron deficiency anemia refractory to oral iron therapy one year post LT. At age 5 years, she had recurrent severe bleeding per rectum requiring multiple blood transfusions associated with mild thrombocytopenia. The investigations revealed negative celiac profile and normal gastroscopy, small bowel enteroscopy including the Roux-en-Y limb, and capsule endoscopy. Selective arteriogram during the severe bleeding also failed to identify the source of GI bleeding. CT angiogram done during the time of bleeding revealed partial portal vein thrombosis with collateral around the duodenum. Continuous intravenous esomeprazole and octreotide failed to control the bleeding. Because of the life threatening recurrent bleeding, thalidomide was initiated at 3 mg/kg orally once daily. The bleeding stopped immediately with no recurrence of bleeding or need for blood transfusion during the four months period of thalidomide prescription. The child has remained free of GI bleeding episodes during the follow up four months period following stopping thalidomide. Thalidomide was not associated with any adverse side effects.

Conclusion: Thalidomide is safe and effective to treat obscure GI bleeding in children. Large case series studies are needed to support our observation.

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Prevalence of eosinophilic esophagitis in adolescents with esophageal atresia

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Objectives and Study: Recently, cases of Eosinophilic esophagitis (EoE) occurring in patients with esophageal atresia (EA) have been reported, although the exact prevalence of EoE in EA remains unknown. To investigate the prevalence of EoE among EA in adolescents and to describe these patients’ characteristics.

Method: Systematic upper gastrointestinal endoscopies with multistage esophageal biopsies were prospectively performed in 63 adolescents with EA. A standardized form was used to collect clinical and endoscopic data. In patients with “proven EoE”, EoE diagnosis was made following the 2007 recommendations: ≥15 intraepithelial eosinophils/high power field (HPF) while treated with proton pump inhibitors (PPI). In a second group (Eo ≥15), EoE was identified in patients with ≥15 intraepithelial eosinophils/HPF, whatever the response on PPI therapy.

Results: Six patients presented 17 to 100 eosinophils/HPF; among them, three patients treated with PPI had proven EoE. An atopic condition was reported more frequently in the Eo ≥15 group than in patients with no EoE (66% vs 16%; P = 0.014). Except for chest pain, symptoms and endoscopic features were similar in patients with Eo ≥15 and patients with no EoE.

Conclusion: The prevalence of EoE is high in adolescents with EA. Our study highlights the importance of considering EoE in patients with EA and the use of multistage biopsies to identify EoE.
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G-P-145

Interactions between gut microbiota and immune repertoires among intestine transplant patients after administrations of probiotics

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Objectives and Study: Small bowel transplantation (SBT) is a life-saving procedure for patients without sufficient bowel length to absorb enough nutrients to survive. However, the role of the microbiota in these severely immune-suppressed individuals is unknown. The aim of this study was to investigate the changes of gut microbiota and immune repertoires in SBT patients.

Method: The SBT patients without obvious sepsis, weaning from parenteral nutrition (PN) and normal oral intake were enrolled in this study. These SBT patients received oral probiotics (Clostridium butyricum MIYAIRI 588, 1.5 x10⁹ CFU/day) for 1 month. Fecal and blood samples were collected at before, 1 week and 1 month after oral probiotics therapy. Next-generation sequencing targeting 16S ribosomal sequences from fecal materials and CDR3 nucleotides from whole blood was used to evaluate gut microbiota and immune repertoires, respectively. We used linear mixed model to compare the changes of microbiota before and after probiotics treatment.

Results: Eighteen samples were obtained from 6 SBT recipients before and after probiotics treatment. These SBT patients had no obvious sepsis and no rejection during this period. Analysis based on the family level, SBT patients before probiotics treatment had a higher proportion of Enterobacteriaceae. After probiotics treatment, Bacteroidaceae and Veillonellaceae increased from 1% to 19% and 6% to 12%, respectively. Instead Enterobacteriaceae and Lactobacillaceae decreased from 50% to 30% and 22% to 15%, respectively (p <LT; 0.05). The most characteristic alterations were decreases of Enterobacteriaceae and increases of Bacteroidaceae at the family level. Corresponding changes in immune repertoires were located in IgA but not in IgG or γδ-T cells. The diversities of IgA repertoires, unlike fecal bacteria, decreased with probiotic intake.

Conclusion: In conclusion, we provided direct evidences of probiotic-induced interactions between gut microbiota and immune repertoires among intestine transplant recipients. A beneficial role of probiotics in diversifying gut microbiota and potential uses of IgA repertoires to monitor microbe dynamics were clearly demonstrated.

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Objectives and Study: Around 25% of children with Short Bowel Syndrome (SBS) had experience of food aversion (FA), which can have implication for weaning off parenteral nutrition (PN). The aim of this study is to assess the efficacy of a play therapist intervention to get over FA.

Method: Retrospective analysis of all children with SBS referred to the Paediatric autologous bowel reconstructive unit (PABRU), Royal Manchester Children's Hospital (RMCH) were performed from 2004 up to date. Inclusion criteria were SBS patient suffering from FA and managed with MPT. FA was classified through symptoms such as gagging, retching, vomiting and refusal of oral feeds/ fluids. Food was categorized by tastes and textures. Statistical analysis was performed by McNemars test.

Results: Twelve children with SBS who underwent autologous gastrointestinal reconstruction procedures (AGIR) were identified (4 M, 34%) and underwent messy play therapy (MPT). All patients had safe oral motor skills, and all children had been exposed to some oral feeds prior to commencing messy play, and all had been receiving parenteral nutrition from birth. Small bowel length at referral was 36.67 ± 31.8 cm. Aetiology of the SBS in this population varied from complex gastroschisis and necrotising enterocolitis (NEC) to small bowel atresia, volvulus and Hirschsprung’s disease (HD). After surgical treatment the bowel length rose to 70.17± 61.6 cm. The mean age of starting messy therapy was 16 months and average duration 10.25 months. Mean age of completing therapy was 26.25 months. Before MPT only 25% patients tolerate more than 1 taste category. McNemars test showed significant improvement in savoury (p=0.001), sweet (p=0.002) and mixed texture (p=0.001) food intake. The end of the treatment achieved tolerance to an oral diet achieved in all patients.

Conclusion: This study has shown that MPT is an effective intervention for SBS patient with FA. All the children have gone from not tolerate to a full oral feeding. Socially the children are now able to enjoy mealtimes with family. Further studies should incorporate a comparison between the various methods with a strict definition for 'success', along with an assessment of anxiety in both the child and parent, pre, during and post treatment.

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Cow’s milk allergy in infants referred to a specialized ambulatory in gastropediatrics

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Objectives and Study: Cow’s milk allergy (CMA) is described in 5.4% of the patients followed in the outpatient clinic of gastropediatrics, but the suspicion has become more prevalent in our country. The infants represent a good part of this, and a greater knowledge of this population is necessary.

Method: Retrospective and descriptive study was carried out by the collection of data from the medical records of infants referred for suspected CMA, followed at a tertiary outpatient clinic.

Results: We evaluated 92 infants referred with suspected cow’s milk allergy at the age of the first clinical presentation between 1 day and 10 months of life (average of 2 months and median of 1m). The most frequent complaint was hematochezia in 57% (52/92), followed by diarrhea in 28% (26/92), vomiting in 24% (22/92), dermatitis in 15% (14/92), and urticaria in 6% (6/92), abdominal distension in 6% (6/92), dehydration with or without shock in 5% (8/92), bronchospasm in 4% (4/92) and malnutrition in 5% (5/92). In 69 patients the oral provocation test (OPT) was performed to confirm the diagnosis, which was positive in 21 patients. The symptoms presented in the OPT were diarrhea (8/21), vomiting (8/21), urticaria (5/21), stool blood (4/21), dehydration (3/21) and perioral erythema (3/21). Exclusion diet time until TPO ranged from 1 month to 108 months (average of 9 months and median of 10 months).

Conclusion: The most frequent complaint was hematochezia, and after the OPT, most of the diagnoses were not confirmed (70% of the tests were negative), or they had been in the formulas for an average of 9 months, and they were tolerant.

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Levels of fecal Calprotectin in patients with food allergy in paediatric nutrition and gastroenterology center of Colombia (Gastronutriped)

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Objectives and Study: Fecal calprotectin (FC) is a very sensitive but not very specific marker of intestinal inflammation, which is becoming more important day by day as a tool for the diagnosis and monitoring of pathologies of inflammatory origin. Several studies have been conducted on the role of FC in the diagnosis and monitoring of patients with food allergy. The objective was to evaluate the level of FC in patients with different types of food allergy (FA) in paediatrics. Descriptive retrospective study 2013-2017.

Method: Patients ≤ 18 years of age were included, who were diagnosed with food allergy in Gastronutriped and FC was performed. The FC values were classified according to the National Institute for Health and Care Excellence (NICE) guideline: negative if it was less than 50 µg/g, 50-100 µg/g; moderate 101-200 µg/g and severe >200µg/g. FC was processed by Immunoassay. The data were analyzed in Stata 13. For the categorical variables, absolute and relative frequencies were used and the continuous variables were analyzed under central tendency and dispersion measures. Chi square test, CI 95% and P ≤0.05 were used.

Results: 25 patients included, the median age was 24.5 months (interquartile range 59.5 months). 54.17% were male. 72.22% of births were C-section. 80% had Non-IgE mediated food allergies and the main diagnosis was allergic enteropathy (65%). 20% were mixed allergies, mainly eosinophilic gastroenteritis in 80%. No patients with IgE-mediated food allergy were found. The median of FC was 86.5 µg / g (interquartile range 197.65 µg/g). The median FC in mixed food allergy was 65.7 µg / g (interquartile range 170.25 µg/g) classified in moderate range and for Non-IgE mediated food allergies was 87.6 µg/g (interquartile range 153.8 µg/g) which was classified within the slight level. Comparing the immunological mechanism of the food allergy and the FC values, no statistically significant difference was found (p = 0.241).

Conclusion: We found abnormal values of CF in mixed and cells mediated FA. FC could be useful as a noninvasive test to give support to the gastrointestinal symptoms suggestive of FA, but their ranges do not seem to be specific to determine the type of FA. We recommend studies with other Food Allergy Reference Centers with a larger sample of children in order to determine the FC range between the different types of FA.

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Vitamin C deficiency in Orange County FL

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Objectives and Study: Scurvy, or hypovitaminosis C, is a rarely encountered disease in the pediatric population in developed countries. Humans and primates lack the ability to synthesize vitamin C, as the enzyme is inactive, thus making ascorbic acid an essential dietary nutrient. Vitamin C is a cofactor in the synthesis of several molecules including collagen, steroids and neurotransmitters. Deficiency leads to multiple systems being affected. The characteristic dermatologic findings are follicular hyperkeratosis, petechial hemorrhages, easy bruising, swollen/bleeding gums and the musculoskeletal symptoms of bone pain, arthralgias, abnormal gait and refusal to bear weight. Anemia can be present and can be attributed to defects in collagen synthesis-this will lead to acute blood loss-either into soft tissue locations, muscles, joints and/or the GI tract.

Method: We present a case in a 9 year old child with autism and food selectivity. She had multiple visits to the hospital, her pediatrician and orthopedist due to musculo-skeletal complaints and was admitted with severe anemia to the hospital. Due to concerns for possible Inflammatory Bowel disease or GI hemorrhage, Gastroenterology was consulted.

Results: 9-year-old female from Orange County FL with autism, constipation and severe food selectivity was admitted due to progressively worsening musculoskeletal complaints and severe anemia (hemoglobin 5.8 g/dL). Physical examination was notable for perifollicular hemorrhages on the lower extremities, gingival hyperplasia, and inability to ambulate due to pain with weight bearing/flexion of her lower extremities. She had presented over the previous 2 months to her General pediatrician as well as an orthopedist and had been hospitalized a month prior to this admission due to similar complaints. Rheumatic labs had already been ordered and hemoccult and lactoferrin stool testing were positive. Pediatric Gastroenterology was subsequently consulted. Dietary history revealed that she only ate pancakes and macaroni and cheese. No fruits/vegetables or any foods containing Vitamin C. Highest concern was for scurvy (Vitamin C deficiency), but there were also concerns for possible Inflammatory Bowel Disease or other GI sources of bleeding. IV vitamin C was started empirically after level was drawn. Endoscopy/Colonoscopy revealed normal gross upper endoscopy but lower endoscopy was impressive for what appeared to be submucosal hemorrhage most notable in the sigmoid colon. Vitamin C level returned as less than 0.1 mg/dL a few days later. Mucosal biopsy results were normal. The patient improved during the hospitalization, was transitioned to oral Vitamin C, and at 3 week follow-up with Gastroenterology, she was running and jumping again.
Conclusion: Scurvy continues to be an infrequently encountered condition in the pediatric population and the take home point of this report is to maintain awareness of nutritional deficiencies, especially in at risk individuals with restricted diets.

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Objectives and Study: Cow’s milk protein allergy (CMPA) is the most common food allergy in the first year of life. A great proportion of children acquire tolerance before the age of 3 years, when a stable adult-like gut microbiota is being established. Associations between CMPA in infants and altered intestinal microbiota structure have been previously pointed out. However, non-IgE mediated forms remains poorly understood and are less studied than IgE mediated ones. Current guidelines recommend the use of extensively hydrolyzed formula (EHF) for CMPA as first choice, but other formulas based on vegetable proteins are also employed in daily practice. The aim of our study was to give clues on the role of type of feeding, microbiota composition and sensitization in non-IgE CMPA children.

Methods: Eighteen infants between 1 and 2 years old, diagnosed with non-IgE CMPA (clear positive oral challenge and a negative skin prick test) were recruited at different regional hospitals in Northern Spain (Asturias). They all were on exclusion diet and provided stool samples for the study. A detailed medical history, including type of feeding and formula used were recorded by the clinicians. After six months of milk exclusion a standardized oral challenge was performed under medical supervision. A control group of 10 age-matched healthy infants with normal diet consuming milk proteins were included in the study. Fecal samples of both groups were analyzed by high-throughput DNA sequencing of 16S rRNA gene amplicons (Illumina technology).

Results: Five of the eighteen CMPA infants were fed vegetable protein-based formulas. Of these, three were fed rice formula and, interestingly, none of them developed tolerance. These three children presented a clear distinct microbiota colonization pattern, characterized by a low abundancy of *Bifidobacteria* (less than 0.25% of assigned reads) and clustered separated from those CMPA infants who were consuming EHF and were tolerant to cow’s milk after the challenge. Differences in the composition of the gut microbial communities between CMPA and healthy children were also observed. Non-allergic infants under unrestricted diet showed a significantly higher proportion of *Bacteroides* \((p=0.001)\) as compared to CMPA infants.

Conclusion: Formula and type of feeding can determinate gut microbiota colonization and influence food allergy resolution and tolerance acquisition in non-IgE CMPA cases during the first two years of life.

Disclosure of interest: JJ Diaz have received speaker fees from Mead Johnson Nutrition, Nestlé, Nutricia, Ordesa and Alter laboratories C Bousoño have received speaker fees from Mead Johnson Nutrition, Nestlé, Nutricia and Ordesa laboratories S Jimenez have received speaker fees from Nutricia laboratories

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Prevalance, clinical features and prognosis of food protein-induced allergic proctocolitis

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Objectives and Study: Food protein-induced allergic proctocolitis (FPIAP) is characterized by fresh bloody stool accompanied by moderate gastrointestinal symptoms, usually seen in well-appearing and exclusively breastfed infants. Despite its benign nature, FPIAP can cause great anxiety in parents, about the nutritional status and the growth of the infant, because of dietary interventions. In this study, we aimed to determine the prevalence, the clinical properties, the natural course and the factors that affect the tolerance development in patients with FPIAP.

Method: The clinical symptoms, offending factors, laboratory findings, methods used in the diagnosis and tolerance development for 123 patients with FPIAP, followed in the pediatric allergy and gastroenterology clinics, were examined in our retrospective cross-sectional study.

Results: The prevalence of FPIAP is 0.01 %. Main symptoms are bloody stool in 74.8% and mucous stool in 99.2% of the patients. The age of onset is 2.69 ± 2.31 months. Major food involved is Cow's milk (%99.2). Other foods found as offending substances are egg in 37.7%, wheat in 6.5%, nuts in 1.6% and fish/seafood in 0.8% of the patients. Single food allergy was 62.6% and multiple food allergy was 37.4%. 51.2% of the patients developed tolerance at age 1, 37.4% at age 2. Only 11.4% of the patients developed tolerance after 2 years and the latest age of tolerance was 4.

Conclusion: Multiple food allergy is related with poor prognosis. Although the infrequency, high levels of serum milk and wheat specific IgE are found to be related with late tolerance development. Atopy patch and skin prick tests are positive in 1/3 of the patients, but they are not associated with the prognosis. Breastfeeding should be encouraged for infants with FPIAP, patients receiving breast milk shorter than 6 months showed poor prognosis, only 26.7% of them achieved tolerance at the age 1.

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Association between atopic march diseases and the functional disorders of the gastrointestinal tract

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Objectives and Study: Atopic march (AM) is composed of atopic dermatitis (AD), perennial allergic rhinitis, or seasonal allergic rhinoconjunctivitis (PAR, SARC) and bronchial asthma (BA) - is diagnosed in about 20% of the individuals of the world’s human population. Over the past 20 years, a second epidemic wave of AM, mainly associated with the presence of food allergies, rages in Europe. Pathophysiogically Without precise diagnostics and effective management the AM trends to progress at children with age. Whereas the new concept considers the association of AD with functional gastrointestinal tract disorders (FGITD), particularly with functional disorders of the bile system (FDBS), pancreatitis (P). Still, the evidence for such associations is not significant enough to be included as a separate unit in guidelines for AD management. Respectively, the aim of study was to determine the associations between the AM diseases, age and the FGITD.

Method: We analyzed the case histories of 790 children with AM, who were hospitalized in the municipal allergologic center of Dnipro city, Ukraine, during the year 2016. The distribution of groups by age was heterogeneous: 0-3 years - 6.20%, 3-6 years - 22.91%, 7-11 years - 36.08%, 12-18 years - 34.81%. The average age of hospitalized children was 9.5 years (median - 9.0), the youngest patient was 10 months old, and the eldest - 17 years. The case histories with comorbid AM disorders and FGITD - FDBS and P had been distinguished. We had applied the following statistic criteria to verify the data obtained: Spearman-ratio (SR), Student’s t-test (STT) and p-value to evaluate the statistical significance of the results.

Results: The data obtained in the study was contradictory. We obtained the direct associations between the AD and FGITD - FDBS, P. Thus, AD had direct association with FDBS with SR = 0.139 (t(N-2) =3.949, p-value &LT; 0.5), P found it = 0.070 (t(N-2) =1.975, p-value &LT; 0.5). SARC had direct associations with children’s older age - it had been diagnosed more frequently in patient groups aged 6-11 and 12-18 years old (SR=0.218, (t(N-2) =6.282, p-value &LT; 0.5). The association with FDBS and P revealed as negative (SR=-0.113, (t(N-2) =3.193, p-value &LT; 0.5 and SR=-0.072, t(N-2) =2.037, p-value &LT; 0.5 respectively). PAR had revealed the direct association with age - it had been diagnosed more frequently in patient groups aged 6-11 and 12-18 years old (SR=0.077, (t(N-2) =2.160, p-value &LT; 0.5); along with that there had been revealed the negative association with FDBS (SR=0.075, (t(N-2) =2.111, p-value &LT; 0.5). And, as the final step of AM, the BA found association directly with the older age groups - it had been diagnosed within ages 6-11 and 12-18 years old mostly (SR=0.260, (t(N-2) =7.559, p-value &LT; 0.5); and no significant association had been identified between BA and FDBS or P.

Conclusion: There is the significant direct association between AD as the first step of AM and FGITD - FDBS and P. There is no significant association between SARC, PAR and BA with FDBS or P at children. SARC, PAR and BA had found a direct significant association with ages 6-11 and 12-18 years old.

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The relationship between length of viable small bowel and time taken to wean from parenteral nutrition in paediatric patients: A single centre retrospective study

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Objectives and Study: Several single centre retrospective studies report a correlation between length of time taken to wean from Parenteral Nutrition (PN) and length of small bowel (SB). The aim of this study was to compare infants with Short Bowel Syndrome (SBS) within our cohort with the literature. The objectives were to determine:
1. Length of time taken to achieve enteral autonomy for patients with Intestinal Failure (IF) due to SBS
2. If length of SB remaining effected time taken to achieve enteral autonomy

Methods/subjects: Data was collated on all patients with IF (on PN for >28 days) between 2011 and 2017. Information on primary diagnosis, comorbidities, gastrointestinal anatomy (length of SB remaining, presence of ileocaecal valve (ICV) / colon, number of anastomoses), sex, gestational age, and length of time on PN was collected from medical notes and previous databases. Any patients with insufficient background information were excluded.

Results: Seventy three patients with IF were identified; of these 32 (44%) presented with SBS. A total of 27 patients with SBS (59% male) were included in the audit (two excluded due to transfer out of area and three excluded due to insufficient information on anatomy). Eighty one percent were born prematurely and necrotising enterocolitis (NEC) was the commonest cause for SBS in this cohort (70%).
Eighteen infants with SBS (67%) achieved enteral autonomy (Group A) and nine (33%) remain on home PN (Group B). The average length of remaining SB was 52cm (range 22cm-81 cm) in Group A, compared with 42 cm (range 8-80 cm) in Group B. The ICV was present in 61% of Group A and 56% of Group B. In cases where ICV was preserved usually the whole colon remained intact. Only two cases had &LT; 1/3 colon remaining, both in Group B. The average number of anastomoses for Group A was 2.5 (range 1-10) compared with an average of 2.1 (range 1-5) for Group B. The patient with 10 anastomoses weaned from PN in 208 days (6.7 months).
Average time to wean from PN was 565 days (18.2 months), with a range of 172-1865 days (5.5 months- 5.1 years). For patients >50 cm of SB, 8 of 10 (80%) achieved enteral autonomy before 12 months of age. For patients with 20-50 cm SB remaining, two weaned off in &LT; 182 days (6 months) and two by 700 days (23 months). Four remained on PN for > 24 months (3-5 years of age); three of the four had a primary diagnosis of gastrochisis. During this study period, none of the patients with &LT; 20 cm viable SB were successfully weaned off PN. In Group A, one patient required a SB transplant, two required steroids for comorbidities and one underwent serial transverse enteroplasty (STEP). In Group B three patients underwent STEP.

Conclusion: This study confirms the correlation between length of viable SB and time taken to achieve enteral autonomy, as published in previous literature. In this small cohort, there did not appear to be any correlation between presence/absence of ICV and time to achieve enteral autonomy. Neither did the number of enteral anastomosis. Unfavourable prognostic factors for achieving enteral autonomy included &LT; 50 cm viable SB, and less than 50% remaining colon. The presence of GI dysmotility (as seen in gastrochisis) and co-morbidities such as congenital heart disease can prolong the intestinal rehabilitation process.

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GASTROENTEROLOGY - Gastroenterology other

G-P-154

The association between gastrin and iron deficiency in children with Helicobacter pylori infection

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Objectives and Study: H. pylori infection leads to chronic inflammation of the gastric mucosa. Iron deficiency and iron deficiency anaemia are major complications in some children with H. pylori infection. Iron absorption could be compromised by the decrease of parietal cells and reduced acid production hypochlorhydria. A low intragastric acidity increases the serum levels of gastrin. The role of hypochlorhydria and hypergastrinemia in iron absorption in H. pylori-infected children remains unclear. In this study, we aim to analyse the serum gastrin and the iron profiles in children with H. pylori infection.

Methods: An observational retrospective study was performed in 32 children, mean age 15 years (5-18), 18 males, who underwent diagnostic upper-gastrointestinal endoscopy for various dyspeptic symptoms, recurrent abdominal pain, vomiting and iron deficiency anaemia. Gastric biopsies were taken in antrum and corpus, for histologic, bacterial culture and PCR assessment. Histological analysis of H. pylori, chronic inflammation, activity, atrophy, and intestinal metaplasia were noted. H. pylori infection was considered for gastric biopsies with positive histology and/or culture / PCR. Fasting serum samples were also analysed for gastrin, iron, ferritin and haemoglobin before and after eradication treatment. Patients with other gastrointestinal pathology or severe systemic disease were excluded.

Results: The most common endoscopic findings were congestion (84.4%), nodularity (46.9%) and mucosal atrophy (25%). Histologically, 81.3% had signs of chronic gastritis of the body and antrum, and of these, 65.4% with signs of activity.

In 15.6% of the cases, there were signs of glandular atrophy in the body and antrum. None showed signs of intestinal metaplasia.

Of the 4 children with high pre-treatment serum gastrin values (maximum 593 mmol / L), all had low hemoglobin values (minimum 7.3 g / dL). There was no associated glandular atrophy. It was verified with the eradication treatment significant improvement in mean hemoglobin (11.4 g / dL vs. 13.2 g / dL), ferritin (29.4 ng / mL vs 33.1 ng / mL) and gastrin (64.9 mmol / L vs. 46.6 mmol / L). Through the urease respiratory test an eradication rate of 87.8%.

Discussion: We did not identify any relation with elevated gastrin levels and signs of glandular atrophy in histology. Anemia is an important manifestation of Hp gastritis and is associated with elevated levels of gastrin, and this relation was verified in our study.

With the Hp eradication treatment, we observed a significant improvement in the mean values of hemoglobin, ferritin and gastrin, as described in the literature.

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Neuronal transglutaminase, TG6 antibody: Is it positive in autistic children?

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Objectives and Study: Autistic disorder is a spectrum (ASD) of childhood neurodevelopmental disorders characterized by marked inadequacies in the social, communicative, and limited, repetitive behaviors that begin in early childhood. Increase in intestinal permeability which is discussed in the pathogenesis of autism may play a role in gluten sensitization in autistic children. Increased response to gluten peptides (anti-gliadin and anti-endomysial antibodies) with normal mucosa has been shown in some of the autistic patients (1). Neuronal transglutaminase 6 (TG6) is thought to be a more specific auto-antigen for neurological manifestations and known to be associated with gluten ataxia (2). In our study, we aimed to establish anti-TG6 positivity in autistic patients.

Methods: We enrolled 40 autistic patients and 40 healthy children in this study between August 2016 and September 2017. Patients with a known acute and chronic gastrointestinal disease, those with a gluten and casein free diet over the past year, neurological or metabolic comorbidities, allergic, inflammatory and autoimmune diseases were excluded from the study. In both groups we excluded Celiac disease by studying tissue-transglutaminase 2 (anti-TG2) IgA / IgG. Anti-TG2 IgA / IgG and Anti-TG6 IgA / IgG antibodies were determined by using enzyme linked immunosorbent assay (ELISA) (Euroimmune and Zedira, Germany). A result >41 U/mL for anti-TG6-IgA and >44 U/mL for anti-TG6-IgG was considered positive. Equivocal results were in range 26-41 U/mL for anti-TG6-IgA and 28-44 U/mL for anti-TG6-IgG.

Results: The mean age of patients was 7.8 ± 4.5 (10 females, 30 males), and the mean age of controls was 11.6 ± 4 years (22 females, 18 males). Anti-TG6-IgA and IgG were all negative in both autistic patients and healthy controls. Anti-TG6-IgA level of one autistic patient (32.8 U/mL) and anti-TG6-IgG levels of two healthy controls (32.4 and 30.4 U/mL respectively) reached equivocal ranges. The mean results of anti-TG6-IgA / IgG for patients and healthy controls were 3.2 ± 5.4 / 6.1 ± 5.5 and 4.1 ± 3.2 / 10.2 ± 7.7, respectively.

Conclusion: Antibodies against transglutaminase 6 can be identified with different gluten-associated neurological disorders. There is only one study in the literature about TG6 and autism which was reported by Jozefczuk et al (3). They had studied serum samples of 77 ASD patients for anti-TG6-IgA and IgG. 5 patients had positive values (4 for anti-TG6-IgA / 1 for -IgG) with normal mucosa, 3 of them had also AGA IgG positivity, they had pointed that neural TG6 positive patients should be rather classified as non-celiac gluten sensitivity. In our study, no positivity of anti-TG6 antibodies was detected. As a conclusion new clinical studies containing more patients may help to evaluate TG6 antibody levels with ASD.

References:

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Paraneoplastic pemphigus in a child with post transplantation lymphoproliferative disease (PTLD) after short bowel transplantation


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Objectives and Study: Paraneoplastic pemphigus (PNP) is a severe autoimmune mucocutaneous syndrome characterized by blistering due to antibodies against plakins, desmogleins and other components of the desmosome and hemidesmosome. PNP occurs in association with several lymphoproliferative and hematologic neoplasms. There are no reports in the literature of PNP associated with malignancies after solid organ transplantation. About 30% of PNP patients develop respiratory failure with features of bronchiolitis obliterans (BO). This complication is responsible for a mortality rate of 79-83% in children with PNP and pulmonary involvement.

Methods: We describe the first case of PNP in a girl with PTLD after short bowel transplantation.

Result: A currently 10 year old girl was born with severe protein losing enteropathy and intestinal motility disorders. Because she was diagnosed with a partial/atypical microvillus inclusion disease and she was fully dependent on parenteral nutrition, she underwent a short bowel transplantation at the age of 3.5 years. At the age of 9 she was found to have a homozygous Acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1) mutation as the cause of her enteropathy. Ten months after the short bowel transplantation she developed an Epstein-Barr Virus associated PTLD under tacrolimus and prednisolone. Within 6 months she achieved complete remission after Rituximab and chemotherapy. At the age of 7 years she increasingly suffered from painful lesions on her tongue. Dermatological examination revealed a severe oral blistering mucositis, palmoplantar keratoderma and lichenoid lesions on her extremities and trunk (figure 1). In addition to the clinical features (severe stomatitis and PTLD), laboratory tests pointed towards a PNP: (1) direct immunofluorescence of perilesional mucosa and healthy skin showed deposition of IgG in an epithelial cell surface (ECS) pattern and deposition of IgG, IgA, and C3 along the basement membrane zone in a linear pattern; (2) Indirect immunofluorescence showed IgG deposition in an ECS pattern on rat bladder epithelium, and (3) antibodies against the desmosomal protein desmoglein-3 were detected by ELISA. However, we did not find PNP specific cell surface antigens of the plakin family with immunoblotting and immunoprecipitation. Endoscopy also revealed blistering PNP lesions of the esophagus. Additional investigations showed no recurrence of her PTLD. No other malignancies were found. Her treatment of the PNP consisted of high dose prednisolone and one gift of Rituximab to down-regulate her cellular and humoral immune response. Three years after the diagnose her PNP is still active without excessive pain symptoms. She is still treated with tacrolimus (trough levels 3-7 ug/L) and prednisolone. Although she is still suffering from pulmonary complications (recurrent infections, bronchiectasis, ventilator injury), we have insufficient arguments (based on CT imaging) to diagnose her with BO.

Conclusion: PNP in children often presents with typical cutaneous lichenoid lesions and oral/intestinal blistering mucositis. This unique case shows that it also must be considered in patients with associated malignancies after solid organ transplantation. Bronchiolitis obliterans is a feared complication.
Figure 1 - (A) typical (palmo)plantar keratoderma of the fingers. (B) severe erosive mucositis of the lips with blistering lesions of the tongue and (C) esophagus. (D) DIF of healthy skin with IgG depositions in an ECS pattern and deposition of IgG along the BMZ. (E) IF on rat bladder epithelium showing IgG deposition in an ECS pattern. (F) Partial splitting of esophageal epithelium (arrow), intraepidermal lymphocytes and an apoptotic epithelial cell (square).

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Introduction: Megaloblastic anaemia is caused by impaired DNA synthesis during red cell development, resulting in the production of unusually large red blood cells (macrocytes). Megaloblastic anaemia can be due to deficiencies in cobalamin and folic acid metabolism, drugs that inhibit DNA synthesis, and reduced availability of cobalamin and folic acid. The incidence in the United Kingdom is infrequent and is supposedly less than 5 cases in 10,000 individuals. The two cases mentioned below will reveal significant megaloblastic anaemia secondary to specific drug use.

Case Reports: A 15-year-old boy was diagnosed with Ulcerative Colitis (UC) in 2014. In 2016 he relapsed and on reassessment was diagnosed with Inflammatory Bowel Disease of Unclassified Type. He was commenced on Azathioprine and Infliximab in November 2016. In April 2017 he presented with an acute onset of anaemia with no history of blood loss. Blood film revealed megaloblastic anaemia; red cells include oval macrocytes. His vitamin B12 and folate were normal. It was thought to be Megaloblastic anaemia secondary to drug; ie Azathioprine. Then patient’s anaemia improved upon cessation of Azathioprine.

A 9-year-old girl was diagnosed with Crohn's disease in June 2017. She was initially commenced on high dose Prednisolone as endoscopy was suggestive of UC however, histology revealed a single granuloma consistent with Crohn's disease. She failed induction of remission with steroids so Infliximab and 6-Mercaptopurine (6-MP) were commenced. In October 2017, she was readmitted to hospital with active colitis and worsening bowel symptoms. A repeat upper and lower endoscopy revealed pancolitis and a diagnosis was revised to Inflammatory Bowel Disease Unclassified (IBDU). Exclusive enteral nutrition was trialled for 10 days with no clinical change. Despite therapeutic levels of Infliximab, she had relapsed and therefore, Adalimumab was commenced. She later developed acute megaloblastic anemia, leucopenia and neutropenia and on this basis, 6-MP was withheld as the presumed culprit. Her blood film also revealed increased rouleaux, oval macrocytes, rod forms of red cells. Platelets appeared normal, vitamin B12, folate were normal. However, thiopurine metabolites were raised and subsequently, her cell count improved within few weeks after discontinuing 6-MP.

Discussion: Drug related megaloblastic anaemia is not uncommon with use of antimetabolite drugs for the treatment of autoimmune diseases and malignancy. However, it is a relatively rare side effect of Azathioprine use. It is important to recognise that the initial therapeutic effect of Azathioprine may produce longer term adverse effects to the body. Azathioprine is metabolised via 6-Mercaptopurine to its active metabolites. Thiopurine metabolites inhibit glutamine-phosphoribosylpyrophosphate amidotransferase a key enzyme in purine synthesis. These actions are important in inhibiting lymphocyte proliferation in autoimmune disorders; but may also result in toxicity to other blood cell types and tissues. Whilst screening for enzymes involved in thiopurine metabolism such as TPMT one can identify some patients at increased risk of excess toxicity from Azathioprine it will not necessarily identify all at risk.

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Impact of an in-house paediatric surgery unit and human milk centered enteral nutrition on necrotizing enterocolitis

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Objectives and Study: Surgery is still a mainstay in therapy of necrotizing enterocolitis (NEC), but the importance for mortality and morbidity of an in-house paediatric surgery unit remains undefined. Currently the most protective factors are probiotics and exclusive human milk diet, but their relative importance is still unclear. In our study we want to analyse the impact of an in-house paediatric surgery on mortality and morbidity of NEC comparing two tertiary neonatal care centers differing for this factor.

Method: We retrospectively analysed clinical data of 389 consecutive very low birth weight (VLBW) infants with a birth weight ≤1500g. The patients were admitted between 2009 and 2014 in the two almost identical neonatal intensive care units (NICU) at the Children’s Hospital Wuppertal (center 1, n=172) and at the Children’s Hospital Oberhausen (center 2, n=217). The only difference between them was that center 2 comprises an in-house paediatric surgery department, while center 1 relied at the time of the study on a 40km distant paediatric surgery service.

Results: Epidemiological data in the two centers were comparable. Incidence of NEC stage II plus was significantly higher in center 1 (15.1 vs. 5.5%, p=0.0009). This correlated with a significantly lower rate of exclusive human milk feeding compared to center 2 (24.2 vs 59.3%, p<0.0001), whereas probiotic treatment did not differ since both centers used the same product and application regimen. Importantly, when surgical intervention was necessary the portion of removed intestine was significantly shorter in center 2 (19.5 vs. 49.9 cm, p=0.043). Accordingly, the rate of severe short bowel syndrome was substantially lower in center 2 (0 vs 38.9%, p=0.03). Furthermore, Bayley scale long-term morbidity assessment revealed less impaired motoric (delay of -2.2 vs -4.2 months, p=0.21) and psychological (delay of -1.6 vs -4.3 months, p=0.09) development in center 2. Mortality was similar in both centers.

Conclusion: Short- and possibly also long-term morbidity of NEC is clearly associated with the presence of an on-site paediatric surgery unit. An early contact with a paediatric surgeon improves the outcome of VLBW neonates with NEC and a guideline defining the time point for the surgery evaluation needs to be defined. We suggest that a maximal interval of 8 hours after starting the NPO (nihil per os) regimen would be a feasible solution and could improve the surgery outcome. Furthermore our study highlights the relative impact of the feeding regimen on the development of NEC: in the presence of identical probiotics supplementation, enteral nutrition with human milk seems to be a strong protective factor.

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Intestinal permeability is increased in ex-premature children with a history of intrauterine growth retardation

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Objectives and Study: Intestinal permeability (IP) is increased in animal models of prematurity and Intrauterine Growth Retardation (IUGR), suggesting an impaired intestinal barrier integrity leading to weight growth delay. No study exists in humans. We aimed to perform a pilot study to assess IP in a pediatric population with persistent growth retardation and a history of preterm birth and IUGR.

Methods: We reviewed 1356 clinical charts of neonates born prematurely between January 2009 and January 2012. We selected children small for gestational age (SGA), with a documented history of IUGR, persistent height and weight growth delay, no history of congenital, metabolic, gastrointestinal, neurologic, cardiac or surgical diseases. All children performed Lactulose/Mannitol (L/M) ratio test to assess IP.

Results: We finally enrolled 11 patients (7 males, age range 4-8 years), and 10 healthy patients (6 males, age range 8-10 years) for comparison purposes. IP was significantly increased in cases compared to controls (0.0946 ± 0.063 vs 0.0158 ± 0.006, p< 0,05), being pathologically high (> 0.003) in 100% of patients compared to 5% of healthy subjects.

Conclusions: IP is increased in ex-premature children with a history of IUGR, suggesting a role in the persistent growth delay. Further studies on larger series are needed to clarify IP role in the pathogenesis of persistent growth restriction.

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Grafting’s function in patients with liver-intestinal and multivisceral transplantation

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Introduction: There are few studies of the intestinal graft function in medium and long term.

Objectives: Assess the functional status of the graft in transplantation patients, once the immediate post-transplant has been overcome.

Methodology: Patients who received a liver-intestinal or multivisceral transplantation were prospectively evaluated through cross-sectional data collection during a review. Clinical, analytical and functional variables are analyzed. Unstable patients with intercurrent processes were excluded.

Results: Twenty-six patients were analyzed, 65.38% of them male. 21 with multivisceral graft (80.76%) and 5 liver-intestinal (19.23%). 7 multivisceral grafts were retransplantation (26.92%). The average age at transplantation was 1.73 +/- 3.22 years (range: 7 months - 13 years). The average time post-transplant was 3.78 +/- 3.69 years (range 1.5 - 14 years). The indication for transplant was volvulus (19.23%), necrotizing enterocolitis (15.38%), gastroschisis (15.38%), pseudo-obstruction (11.53%), atresia (7.69%) intestinal ischemia (7.69%), epithelial dysplasia (7.69%), MartinezFrías syndrome (3.84%), mitochondrial disease (3.84%) and Hirschsprung’s disease (3.84%). 96.15% of patients are autonomous oral-enteral. 1 (3.85%) maintains home parenteral nutrition. 15.38% receive enteral nocturnal nutrition. 3 patients (11.53%) maintain ostomy. Fecal alpha 1-antitrypsin was normal in 92.30% of patients. Fecal elastase was normal at 100%. Faecal fat excretion was normal in 84.61% of patients, only 4 (15.38%) with a moderate steatorrhea. Blood parameters were normal in 100% of patients, including serum citrulline levels with a mean of 37.16 µmol / L (range 21-74).

Conclusions:
1. Patients with liver-intestinal and multivisceral transplantation have good graft function in medium and long term.
2. Most maintain digestive autonomy.
3. Although in some patients steatorrhea is observed, pancreatic function is normal in 100% of patients with a multivisceral transplantation that includes a pancreatic graft.

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GASTROENTEROLOGY - Gastroenterology other

G-P-161

Spleen implication in pediatric multivisceral transplantation

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Objective: Analyze the role of spleen in pediatric intestinal/multivisceral transplantation and its variants

Material and methods: We analyzed pediatric patients transplanted in our unit from October’99 to May’15. Comorbidities (cellular, humoral and chronic rejection, graft-versus-host disease(GVHD), lymphoproliferative syndrome(PTLD), hematological alterations and death) are analyzed in patients who spleen was included as part of the intestinal graft, in splenectomized patients and those who preserve their native spleen

Results: 103 transplants were performed: 26 Intestinal transplantation isolated, 22 liver-small bowel, 52 multivisceral and 3 modified multivisceral. 79% were first grafts, and 21% were retransplantation (27% third graft). Spleen was included as part of the graft in 11.7% patients, their native spleen was preserved in 50.5% and splenectomy was performed in 37.8%. Analyzing comorbidities, humoral rejection was infrequent; and it’s only present in patients with native spleen(4%), presenting positive antibodies without rejection in 17%, compared to 2.5% of splenectomized. Chronic rejection, it’s 4 times more frequent in native spleen versus splenectomized(OR:4, CI:2-30). None of the patients with transplanted spleen presented chronic or humoral rejection. Cellular rejection is 2 times more frequent in native spleen instead patients with spleen transplanted(OR:2.2, CI:0.5-10.6) and it’s 1.5 times more frequent in splenectomized(OR:1.5, CI:0.3-7.6). GVHD is 6 times more frequent in patients with transplanted spleen than in patients who preserve the spleen(OR:6, CI:2.2-13), followed by splenectomized(OR:2.2, CI:1.5-8.2). PTLD is 1.8 times more frequent in patients who preserve their spleen, compared to splenectomized(OR:1.8, CI:0.6-5.5), followed by patients with spleen transplanted(OR:1.4,CI:0.2-9.9). Haematological alterations are 79% more probably in patients with spleen transplanted (OR:3.8, CI:1-14) and 63% more probably in splenectomized versus those that preserve their native spleen(OR:1.7, CI:0.5-5.8). Death is 87% more probably in patients who include the spleen in the graft, compared to those who preserve their native spleen(OR:6.7, CI:1.8-24), followed by splenectomized in whom death is 87% more probably(OR:5.1,CI:2-13)

Conclusions: Rejection is more frequent in patients with native spleen. Probably due to the confusional factor that supposes the type of transplant performed like the isolated intestinal transplant, not including the liver graft, and is well known the protective factor that this supposes for rejection. Include spleen as part of the intestinal graft is a risk factor to develop PTLD, hematologic alterations and death. So the inclusion of the spleen as part of the intestinal/multivisceral graft is not recommended. Preserve native spleen is a risk factor to develop GVHD. However, it seems to be a protective factor against the development of other comorbidities, so it’s recommended to preserve native spleen whenever is possible.

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The Brussels Infant and Toddler Stool Scale (’BITSS‘): a study on inter-observer reliability


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Objectives and Study: There is agreement that the Bristol Stool Form Scale (BSFS) is not adequate for use in non-toilet trained children. The Brussels Infant and Toddler Stool Scale (BITSS) was developed to overcome this problem. The BITSS consists of 7 color photographs of diapers containing stools of infants and toddlers. Our objective was to evaluate the inter-observer reliability of stool consistency assessment among parents, nurses and medical doctors (MDs) using the BITSS.

Method: We performed a multicenter cross-sectional survey study between 2016 and 2017, inviting parents, nurses, and MDs from 18 countries to participate. Participating centers were instructed to include at least 50 parents, 25 nurses, and 25 MDs. Participants were asked to rate the BITSS photographs according to the images and descriptions of the BSFS. For the individual BITSS photographs, the proportion of exact agreement and the mode of the BSFS type chosen for each photograph were determined. The reliability of the BITSS was evaluated using the overall proportion of perfect agreement and calculation of the Fleiss’ κ statistic.

Trial Registration Number: NCT02913950.

Results: 2,462 observers participated in this study: 1,181 parents (48.0%), 624 nurses (25.3%) and 657 MDs (26.7%). For the overall analyses, 2,352 observers were included. Overall, 819 (34.8%) observers matched all 7 BITSS photographs perfectly with the reference BSFS stool types, and 1647 (70.0%) showed maximum 1 class deviations. The best-performing BITSS photographs were those corresponding with BSFS type 7 (87.5%) and BSFS type 4 (87.6%), followed by photographs representing BSFS type 6 (75.0%), BSFS type 5 (68.0%), BSFS type 3 (64.6%) and BSFS type 1.
(64.8%). The weakest performance was observed for the photographs corresponding with BSFS type 2 (49.7%). The overall κ-value for the BITSS was 0.490 (95% CI 0.37-0.62), corresponding to a moderate agreement. Based on these results, photographs were categorized as hard (BSFS type 1-3), normal formed (BSFS type 4), loose (BSFS types 5&6) or watery (BSFS type 7) stools. Using this new categorization system, all 7 BITSS photographs were correctly matched with the new categories for 1,713 (72.8%) of the observers. For each photo correct allocation into 1 of the 4 categories ranged from 83-96%, with an average of 90% (Table 1). The number of correct allocations of this new grouped BITSS differed significantly among observer groups (MDs 85.3%; nurses 74.8%; parents 64.8%, P < .001) and continents (Europe 79.8%; Asia 62.9%; Americas 65.2%, P < .001).

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<tr>
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<th>Photo 2 (BSS 1)</th>
<th>Photo 5 (BSS 2)</th>
<th>Photo 4 (BSS 3)</th>
<th>Photo 6 (BSS 4)</th>
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<td>Hard (BSS 1-3)</td>
<td>95.9</td>
<td>93.4</td>
<td>96.2</td>
<td>5.4</td>
<td>6.9</td>
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<tr>
<td>Normal formed (BSS 4)</td>
<td>0.9</td>
<td>2.0</td>
<td>1.5</td>
<td>87.6</td>
<td>6.8</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Normal loose (BSS 5-6)</td>
<td>3.0</td>
<td>4.6</td>
<td>2.2</td>
<td>6.8</td>
<td>83.1</td>
<td>89.2</td>
<td>11.2</td>
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<tr>
<td>Watery (BSS 7)</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>3.2</td>
<td>8.6</td>
<td>87.5</td>
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[Proportions of exact agreement for each individual]

**Conclusion:** The BITSS shows moderate agreement with the BSS. After grouping BITSS photographs together, the BITSS is likely to prove useful in the assessment of stools of non-toilet trained children in clinical practice and for research purposes.

Predicting the progress of severe caustic injury to complications: the influence of high doses of corticosteroids in preventing corrosive-induced strictures

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Objectives and Study: Esophageal burn due to corrosive substance ingestion in childhood is a public health issue. The development of long term complication, such as oesophageal stricture, oesophageal dysfunction and gastric outlet obstruction, is the most feared sequelae of caustic ingestion. The utility of corticosteroid in preventing these caustic complications is controversial. The aim of this study was to investigate the risk factors associated with the development of long term complication induced by caustic ingestion (oesophageal stricture, oesophageal dysfunction, gastric outlet obstruction) and to evaluate the effect of high doses of corticosteroids in the management of severe corrosive induced injury.

Method: A retrospective study was done from 1st January 2005 to 31st December 2012, involving children who had severe endoscopic lesions (grade 2 /grade 3)) after a caustic ingestion, in the endoscopy unit of the Tunis infant Hospital. Mucous burns in the esophagus and the stomach were classified according to Zargar classification. We looked for predictors of long term complication in this population and then in the group of children having stage 2b oesophagitis; thanks to univariate and a multivariate study. The data was input on Excel and analyzed through SPSS 20.

Results: We collected 98 clinical records of severe oesophageal and gastric caustic burns. The mean of age was 3.4 years ±2.1 years [1 - 14].The caustic substance was an acid, an alkali, an oxidant in respectively 87 (88 %), 6 (6 %), 5 (5 %) of cases. Severe oesophagitis were noticed in 58/98 (59 %) of cases, it were associated to gastric lesion in 33/98 (34 %) of cases, and severe gastritis were noticed in 7/98(7%). Thirty one patients (32%) developed a caustic long term complication, 21/98 (21%) of cases developed oesophageal stricture, 28/98 (29%) oesophageal dysfunction and 3/98 (3%) of cases a gastric outlet obstruction. Factors significantly associated with caustic complications were in the univariate and multivariate analysis: hematemesis (ORaj=7.01 [1.3-37]; p=0.022), grade 3 lesions of the oesophagitis (ORaj=9.3 [1.3-62]; p=0.021), the duration of treatment by IPP>14days (ORaj=5.38 [1.1-25.2]; p=0.033). Factors significantly associated with development of caustic stricture were hematemesis (ORaj=13.56 [1.1-60]; p=0.038), the extention of oesophageal lesion (ORaj=7.01[1.3-37]; p=0.022); and them associated with oesophageal dysfunction was the duration of treatment by IPP>14 days (ORaj=17.3 [3.8-77]; p&LT; 10-3).Then, concerning the group of patients with stage 2b oesophagitis the independent factors associated with stricture formation was hematemesis (ORaj=10 [1.2-24];p=0.02) and epigastralgia (ORaj=4.4 [1.5-33.8]; p=0.035).

Conclusion: This study did not find a clear benefit of steroid administration in terms of long term complication prevention. Therefore the use of corticosteroid in the management of corrosive ingestions should be evaluated by a prospective studies.
Gastrointestinal vascular malformations in patients with Turner’s syndrome: Systematic review of case reports

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Objectives and Study: The phenotype of Turner syndrome (TS) is relatively well known as the cause of short stature and gonadal dysgenesis associated with other characteristic features of the body appearance. More scanty are the data of other abnormalities associated with TS i.e gastrointestinal (GI) vascular malformations. Therefore, this literature review aimed to characterize the nature of GI vascular malformations in patients with TS, their localization in the GI tract, as well as its clinical and laboratory manifestations, management and outcome.

Method: A systematic search of English articles was conducted using Medline and Embase (both bases up to August 2017). Manual search for the references of included papers was carried out to identify potential additional references. We also conducted a retrospective chart review of all patients with TS and GI bleeding hospitalized in our institution. All studies on GI bleeding due to abnormal GI blood vessel in patients with TS at any age were included into our review.

Results: There were no clinical trials or cohort studies found. A total of 17 articles, published between 1947 and 2015, describing 27 cases were retrieved and reviewed. Mean age of patients with TS at abnormal GI vessels diagnosis was 17.5 years (0.1-57 years). Clinically, vessel abnormalities varied from asymptomatic course (1/27) or iron deficiency anemia (25/26) to GI acute bleeding (12/23). Abnormal GI vessels occurred throughout the entire small bowel, large bowel and mesentery, with a preference for the small intestine (22/26). The most common (21/25) were telangiectasias.

Conclusion: GI vascular malformations in patients with TS were rarely reported in the literature data. Nevertheless, telangiectasias of the small intestine were the most commonly seen GI abnormal vessels in patients with TS.

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Comparison of proteome in human colonic mucosal biopsies preserved by two different reagents or heat-stabilisation

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Objectives and Study: Proteome of colonic mucosal biopsies has recently been started to study in patients with inflammatory bowel disease to get a comprehensive view of the host changes related to the condition. The prompt inactivation of proteolytic enzymes after removal of the biopsy is a critical step in the analysis in order to get reliable findings. The aim of the present study was to compare three different methods of enzyme inactivation in the proteomic analysis of human colonic mucosal biopsies.

Method: The study cohort comprised 10 adults to whom ileocolonoscopy was done on the clinical basis due to gastrointestinal complains or previous pathology. None of the patients had inflammatory bowel disease or colon cancer. Three biopsies situated very close to each other in a non-pathological region of transverse colon were taken from each of the patients for the study. Immediately after the removal the biopsy was preserved either in reagent 1 (RNAlater™; group A), reagent 2 (Allprotect™; group B) or heat-stabilized (by Stabilizer T1™; group C). In the following steps (peptide isolation, purification, identification and quantitation by mass spectrometry) identical methodology was used. Protein quantitation was done by data independent acquisition (DIA) based mass spectrometry method using OpenSWATH software. Peptide identifications were performed using Comet and X!Tandem search engines against UniProtKB/Swiss-Prot human database. Differential expression between the sample groups was determined using reproducibility-optimized test statistic (ROTS).

Results: Total number of different proteins identified were 3068, 2973 and 2995 in the group A, B and C, respectively. Of these, 2794 same proteins (representing 91-94% of all the proteins found in the individual groups) were detected in all the groups. Despite this great similarity in the protein identifications, the group C separated from other groups according to the principal component analysis of the protein quantifications (data not shown). In pairwise comparisons, there were 16 (10 up-regulated and 6 down-regulated), 103 (37 up-regulated and 66 down-regulated) and 191 (78 up-regulated and 113 up-regulated) proteins showing differential expression between the group B versus the group A, the group C versus the group A, and the group C versus the group B, respectively (false discovery rate FDR &LT; 0.01).

Conclusion: High numbers of shared proteins were identified in the human colonic mucosal biopsies by mass spectrometry despite three different preservation methods.

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Evaluation of serum zonulin level and its relationship with gastrointestinal symptom score in children with autism spectrum disorders

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Objective and Study: The frequent occurrence of gastrointestinal complaints in patients with autism spectrum disorder (ASD) leads to growing ideas that brain-gut axis may have an important role on pathogenesis of ASD. There are many studies which have been focused on increasing of the intestinal permeability in ASD. Zonulin is a physiological modulator that controls intestinal permeability by regulating the function of tight junctions. The aim of this study is to evaluate serum levels of zonulin and the relationship of gastrointestinal symptoms with zonulin levels in children with ASD.

Method: Fifty-six ASD patients (age 8.3 ± 4.7) and 55 healthy children (age 9.3 ± 4.4) as a control group were included in this study. Chronic gastrointestinal diseases and obesity were accepted as major exclusion criteria. Both groups were evaluated for age, sex, anthropometric measurements (height, weight and BMI) and serum zonulin levels. Serum zonulin levels were measured using the sandwich enzyme-linked immunosorbent assay. The severity of gastrointestinal symptoms was assessed with the Gastrointestinal Symptom Rating Scale (GSRS) in ASD group. Scale questions were re-evaluated in itself by dividing the symptoms in 3 groups as general symptoms, lower gastrointestinal system (GIS) symptoms and upper GIS symptoms. Median symptom points were calculated for each symptom group and serum zonulin levels were re-evaluated according to these points.

Results: There was no difference between groups in terms of age, sex, height and body weight. Serum zonulin levels were similar in patient and control groups. There was no correlation between zonulin level and age, sex, height, weight and BMI Z score in the control group. A positive and medium level statistically significant correlation was shown between age and serum zonulin level in ASD group (r=0.29; p=0.030). Lower GIS symptoms had the highest percentage (100%) among the subgroups of GSRS in ASD patients. There was a positive and medium level statistically significant correlation between BMI Z score and GSRS total point and lower GIS point (p< 0.001; p=0.009). The zonulin levels of ASD patients whose scores were above the median point in all symptom groups were statistically significantly higher than patients whose scores were under the median point and healthy control group (Table 1).
Conclusion: Although the serum levels of zonulin was similar in ASD patients and healthy controls, increasing in zonulin levels with age and higher intensity of gastrointestinal symptoms was observed in ASD patients. In conclusion, the increase in zonulin levels may play a role in the development of gastrointestinal symptoms in ASD patients.
Fecal microbiota analysis of healthy Korean newborns: Profiles by delivery mode and feeding type

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Objectives and Study: Neonates are born sterile, but many parts of their bodies are colonized by various microorganisms thereafter. The neonatal period is important for the colonization of microflora in the intestines, which is influenced by various factors including the type of delivery mode and feeding. We investigated the effects of the delivery mode and feeding type on the dynamics of gut microbiota in healthy Korean newborns.

Method: One hundred ninety-two healthy term neonates of birth weights which were adequate for gestational age were included in this study. Fecal specimens from newborns were collected at time points of 1 days, 3 days, 7 days, and 14 days after birth. Microbiological composition was examined by next-generation sequencing (NGS) of Illumina MiSeq® system. Comparative analysis was performed composition, alpha and beta diversity of newborns fecal microbiota at the same age across four time points from day 1 to day 14 of age. We also investigated the difference of microbiota composition according to delivery mode and feeding type at the genus levels.

Results: At phylum level, Proteobacteria species were decreased and Actinobacteria species were increased across four time points from day 1 to day 14 of age. At genus level, streptococcus and Escherichia/shigella species were decreased and Bifidobacterium species were increased across four time points from day 1 to day 14 of age. Shannon and Simpson index diversity of alpha diversity were both increased across four time points. The MDS plot of beta diversity at four time points showed a big change on the day 14 from the change on the day 3 and 7. According to delivery mode, cesarean-delivered newborns have higher levels of harmful bacteria, while vaginal-delivered newborns have higher levels of beneficial bacteria. We performed a cluster analysis by dividing by feeding type. There was a big difference between bifidobacterium and Esherichia/shigella between breastfeeding and formula feeding.

Conclusion: The results of this study show that the diversity of gut microbiota according to days after birth and the impact of delivery mode and feeding type on the dynamics of gut microbiota profiles in Korean newborns.

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Inflammatory enterocolitis in paediatric patients with Congenital Chloride Diarrhoea (CCD): a case series

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Objectives and Study: Congenital Chloride Diarrhoea (CCD) is a rare, autosomal recessive disorder caused by mutations in the SLC26A3 gene which encodes a transmembrane chloride/bicarbonate ion exchanger mainly expressed in the apical brush border of the ileal and colonic epithelium. It is characterized by life-long, secretory, chloride-rich diarrhoea, and hypochloraemic, hypokalaemic metabolic alkalosis. Antenatal findings include polyhydramnios and dilated bowel loops. Slightly preterm gestation, lack of passage of meconium and abdominal distension are classical presenting features. Histological evidence of bowel inflammation is not typically seen in CCD[1].

Method: We report 3 cases of CCD with associated bowel inflammatory changes at endoscopy.

Results:
Case 1
Female term infant with antenatal polyhydramnios and dilated, echogenic bowel presented in the first week of life with hyponatraemic/kalaemic metabolic alkalosis and suspected polyuria. Stool chloride was high (116mmol/L). Genetic testing confirmed CCD with SLC26A3 gene mutation (c.2024_2026dup; p.(Ile675dup)). She presented with bloody diarrhoea and elevated faecal calprotectin (395mg/kg) at 7 months of age. Colonic biopsies revealed granulomatous colitis with ulceration, which responded to Prednisolone and Azathioprine.

Case 2
Female, preterm infant (34 weeks') born to consanguineous parents developed severe diarrhoea, vomiting and hypokalaemic metabolic alkalosis with elevated stool chloride (114 mmol/L) at 3 months of age. Genetic testing confirmed the diagnosis (W462X nonsense mutation in DRA gene). Due to persistent diarrhoea and poor weight gain despite electrolyte supplementation, an endoscopy was performed which showed patchy enteropathic changes with villous blunting and borderline increase in intraepithelial lymphocytes and focal active colitis with cryptitis. Calcium butyrate and elemental feed were commenced with favourable clinical and histological response.

Case 3
Term male infant born to consanguineous parents presented in early infancy with watery diarrhoea and weight loss. He was clinically diagnosed with CCD based on elevated faecal chloride (143 mmol/L. and hypokalaemic/hyponatraemic metabolic alkalosis. Histologic examination revealed mild enteropathic changes with apoptotic debris and mild colonic inflammation. These were not treated as not severe and clinically silent.

Conclusion: Our case series highlights the potential association of CCD with enterocolonic inflammation. Early diagnosis and aggressive salt replacement therapy are crucial in CCD management. The clinician should, however, be aware of bowel inflammation as a potential cause of failure of conventional CDD therapy to control bowel symptomatology and the potential need for immunosuppression. Further genetic testing is needed to elucidate the possible link to new genes accountable for bowel inflammation.

A rare cause of iron deficiency anaemia in childhood

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Case Presentation: An 8-year-old boy presented with a few weeks history of lethargy, palpitations and headaches. His haemoglobin (Hb) was found to be low at 49 g/L with a ferritin of 8 ug/L. There was no history of bleeding and no family history of bleeding disorders. There were no other symptoms of note. He was given a blood transfusion and commenced on iron supplements. He re-presented 10 months later with similar symptoms of lethargy and palpitations. Hb had again dropped to 57 g/L. He was referred to the paediatric haematologist at Royal Manchester Children's Hospital for further investigations.

Investigations: Blood tests revealed normal Vitamin B12, folate, renal function, liver function and C-reactive protein. Erythrocyte sedimentation rate was raised at 40 mm/1st hour and orosomucoid 1687 mg/L. Bone marrow aspirate was normal with reactive features. Chest X-ray was normal. Ultrasound abdomen showed 4 rounded hypoechoic lesions in the epigastrium, superficial to the stomach at the tip of the left lobe of liver. The position was atypical for nodes and the largest measured 1.5cm. MR scan abdomen did not demonstrate any abnormality but the scanning was inadequate due to significant artefact movement. An upper GI endoscopy revealed a large sessile gastric polyp at the middle of the greater curvature of the stomach measuring 8-10cm in diameters.

Treatment: He proceeded with surgery and had a wide local excision of the lesion with adequate clear margins. Intraoperatively, he needed a partial gastrectomy due to the size of the lesion, leaving approximately 40% of the stomach.

Result: Histology of the excised lesion showed an ill-defined spindle cell lesion that involves the...
mucosa, submucosa, muscularis propria, serosa and focally some adherent fibrofatty/mesenteric tissue. The histomorphology and immunohistochemical profile confirmed an inflammatory myofibroblastic tumour (IMT). The tumour was completely resected with no evidence of spread outside the stomach or elsewhere. Lymph nodes sampled as part of the surgery were negative. No radiation therapy or chemotherapy was required.

**Outcome and follow-up:** Post-operatively he made a good recovery and was tolerating a full diet. He was discharged with regular follow-up with the oncologist, surgeons and gastroenterologist.

**Discussion:** IMT is a rare spindle cell neoplasm comprising of fibroblasts and myofibroblasts with a non-specific inflammatory infiltrate. IMT is rare and most often affect young adults and children. It has been reported in practically all organ systems with the liver and biliary tract the commonest affected region followed by respiratory tract and gastrointestinal tract\(^1\). Gastric IMT in children is very rare and the available literature comprises of a small number of case reports. Common presentation includes malaise, pallor, weight loss, fever and abdominal pain\(^2\). Primary excision of the tumour remains the most widely reported treatment and is generally successful in effecting long-term cure. Recurrence has been reported and some resulting in death\(^2\)\(^-\)\(^5\). Recurrence mainly treated with further surgical resection and chemotherapy\(^2\)\(^-\)\(^4\). Gastric IMT has an unpredictable outcome and all patients require careful clinical, biological and radiographic follow-up after resection to monitor for recurrence of tumour.

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Multi-locus heterotopic gastric mucosa of the ileum masquerading as Very Early Onset Inflammatory Bowel Disease (VEOIBD) in a newborn

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Objectives and Study: Heterotopic gastric mucosa (HGM) is defined as the presence of gastric mucosa outside the boundaries of stomach documented by histology. Literature suggests that HGM is known to occur in the oesophagus, duodenum, Meckel's diverticulum, ileum, enteric duplication cysts and very rarely outside the GI tract in the mediastinum, scrotum, urinary bladder, airways, and spinal cord. The origin of HGM can be congenital or acquired during the repair process of damaged mucosa but typically confined to one solitary area. The clinical presentation of HGM mostly depend size and location, including pain, bleeding, perforation, ulceration or intussusception. HGM is typically solitary and single, and multi-locus HGM involving extensive GI tract is very uncommon. We report a unique case of multi-locus HGM mimicking VEOIBD with recurrent gastrointestinal bleeding, chronic inflammation and stricturing.

Methods and results: A male newborn presented with bloody stools, diarrhoea, severe hypoalbuminemia and anaemia on day 1 of his life. He was initially treated as necrotizing enterocolitis. His recovery was slow and required prolonged TPN due to intolerance of enteric feeds. Because of recurrent bleeding and ileal obstruction, he underwent ileocecal resection, which showed chronic organizing and perforating ulceration. Ganglion cells were present. Despite this resection, he continued to show ileal obstruction, and underwent another ileal segmental resection upstream due to a stricture. Histology revealed cryptitis, crypt abscess and ulceration made us believe that he had VEOIBD. Extensive work up was done for immunodeficiency (including DHR, anti-enterocyte ab) and VEOIBD genetics (VEOIBD genetic panel for known 28 genes including IL10R and TTC7a). Exome sequencing did not reveal any known pathogenic variants of VEOIBD. He failed medical therapies including steroids and immunomodulator (azathioprine). He continued to require TPN at the age of 2 due to poor enteral tolerance. At 2 years, a MRE showed another ileal stricture. A segmental resection showed heterotopic gastric mucosa scattered throughout the resected ileum for the first time. Although, he has had 2 previous ileal resections and several colonoscopies with biopsies, this was the first time HGM was found. A month after the last resection, he underwent Technetium-99 nuclear scan which showed further presence of gastric mucosa in the remaining ileal loops evident by abnormal tracer intake. Knowing the presence of multi-locus HGM still present, he was started on high-dose PPI therapy. Currently, his TPN is being weaned with advancing enteral feeds.

Conclusion: Our case demonstrates an unusual case of congenital multi-locus HGM of the ileum. The presence of crypt abscess and chronic inflammation mislead us to consider VEOIBD in the differential diagnosis. HGM should be suspected despite absence of histology from resected specimens and biopsies. Increased awareness of HGM as a differential diagnosis is vital with any newborn presenting with GI bleeding. An early nuclear scan may have resulted in exact diagnosis and prevented diagnostic delay.

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Objectives and Study: Long term data on eosinophilic esophagitis (EoE) in children are still lacking. Therefore, this study aimed to compare long term treatment success (clinical and endoscopic) of exclusion diet and topical corticosteroids in the treatment of children with EoE.

Method: This was a retrospective follow-up study conducted in compliance with local ethical board guidelines. All children younger than 18 years of age who were diagnosed from January 2011 until May 2017 with eosinophilic esophagitis (EoE) by a pediatric gastroenterologist, in a tertiary medical center, using standard diagnostic criteria were included into the study. Mean follow-up time was 3 years (range 0.4-6.8).

Results: During the study period 32 children fulfilled inclusion criteria (mean age 11, range 1.1-17 years; 22 male, 69%). Most frequent symptom was epigastric and retrosternal pain presented in 18 (56%) patients, followed by dysphagia in 11 (34%) and improper weight gain in 9 (28%) of patients. Concomitant atopic dermatitis was present in 7 (22%) of patients and respiratory allergies in 13 (41%): asthma in 7 and allergic rhinoconjunctivitis in 6 patients. Majority of patients had nutritive allergies proven with at least one allergic testing (n=24, 75%); 59% had multiple allergies. From allergenic foods main cause was cow's milk protein (n=14), followed by egg (n=11), gluten (n=9), nuts (n=8), fish (n=7) and soy (n=7). Treatment was 6 foods elimination diet in 15 patients (47%), followed by exclusion diet based on allergic testing (n=12, 37%) and corticosteroids (n=5, 16%). In the first six months 67% of patients (n=8) initially treated with exclusion diet based on allergic testing required escalation of therapy to 6 foods elimination diet (n=5) or corticosteroids (n=2) or combination of 6 food exclusion diet and corticosteroids (n=1). From children initially treated with 6 foods elimination diet 4 (27%) patients switched to topical corticosteroids and 5 (33%) children remained on 6 foods elimination diet even 6 months after the diagnosis (meaning that the attempt to introduce excluded foods failed).

From initial cohort 28 (88%) children were followed up for 6 months. From these children 21 (75%) were in clinical (symptom free remission), and from those 10 (36%) were in endoscopic remission as well. Furthermore, after 12 months 27 (84%) patients were still followed up; at that point 21 (78%) children had no symptoms and 10 (37%) children were in clinical and endoscopic remission. From those 10 patients, 2 received no therapy, one received local corticosteroids and 7 received exclusion diet of one or two allergens. There was no association between remission and type of the first therapy, presence of positive allergic tests or history of other atopic disease (not significant for all factors). None of the patients developed EoE related strictures, however, 2 patients whose EoE was in endoscopic and clinical remission (during diet therapy) developed gastroesophageal reflux disease (4.4 and 5.3 years after EoE diagnosis).

Conclusion: The majority of children diagnosed with EoE continue to require dietary modification and/or topical corticosteroid treatment for EoE. Although high proportion of patients had no symptoms endoscopic remission is achieved in limited number of patients.

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STK11 mutations in nine Chinese families with Peutz-Jeghers Syndrome

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**Objectives and Study:** Peutz-Jeghers Syndrome (PJS) is an autosomal dominant hereditary polyposis syndrome, in which germline mutation of the serine/threonine kinase 11 (STK11) is identified in up to 90% of the patients who met clinical criteria for PJS. In this study, we reported two novel mutations and six recurrent mutations in STK11 gene in nine Chinese PJS patients.

**Methods:** Seven sporadic and two familial peadiatric patients who met the clinical criteria for PJS were enrolled in the study from 2014 to 2017. Patients' clinical information on polyp characteristics, polyp-related complications, and family histories were recorded and reviewed. After obtaining informed consent, we performed a mutation analysis of STK11 gene in nine Chinese families targeted next-generation sequencing (NGS) analysis in combination with multiplex ligation-dependent probe amplification (MLPA) assay. Hematoxylin and eosin (H&E) and immunohistochemically stained slides with a human LKB1/STK11 antibody and phospho-AMPKα antibody were evaluated in gastrointestinal (GI) polyps from all PJS patients. Polyps from five cases of juvenile polyp were used as a negative control.

**Results:** The mean age at the onset of GI symptoms was 8.11±2.67 years old, including GI bleeding (1/9), abdominal pain (1/9), prolapsed polyps (1/9), intussusception (4/9), family history of PJS (1/9) and anemia (1/9). These children underwent 58 endoscopy screenings. By NGS of the coding region of STK11 gene, we identified point mutations in 5 patients (Group A) at c.788G>A/p.Leu263Ter (novel nonsense mutation), c.256C>T/ p.Arg86Ter (nonsense mutation), c.734+1G>A (splicing mutation), c.862+1G>G/A (splicing mutation) and c.1062C>G/ p.F354L (missense mutation), respectively. Only one patient in Group A underwent operation for intussusception. By means of MLPA assay, we detected exon deletions in 3 patients (Group B). In details, one patient had exon deletions from 2 to 8 (novel mutation), one patient had deletions of exon 1 and one patient had exon deletions from 1 to 3. All patients in Group B developed intussusceptions and 2 out of them underwent surgery. Patients from Group B developed GI symptoms earlier and more severely than those from Group A. We failed to find any mutation in left 1 patient who met the clinical criteria of PJS. Expression of the STK11 in the PJ polyps was significantly lower than that in controls. The phosphorylation levels of AMPKα paralleled with the levels of STK11 expression.

**Conclusion:** Two novel mutations and five recurrent mutations in STK11 were detected in Chinese PJS patients. The study expands the spectrum of known STK11 gene mutations.

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Objectives and Study: The aim of the study is to establish the features of carbohydrate metabolism in children with pancreatic steatosis evaluated by ultrasound.

Method: We observed 77 children aged 7 to 17 years old, the average age was (11.90 ± 2.83) years. The pancreatic and liver steatosis was evaluated by ultrasonography. According to presence of the obesity/overweight and pancreatic steatosis, children were divided into the following groups: 1 group - 42 children with pancreatic steatosis and obesity/overweight; group 2 - 25 obese/overweight children without ultrasound signs of pancreatic steatosis; 3 group - 10 children with normal weight who had no signs of pancreatic steatosis. The blood serum insulin level was determined by immunoassay, followed by the calculation of the HOMA1-IR, HOMA2-IR with the definition of insulin sensitivity (% S) and beta-cell function (% B). All patients and their parents had given their agreement to participation in the study.

Results: Regarding the level of HOMA1-IR and HOMA2-IR we found that the maximum value was observed in the children with pancreatic steatosis. %B was significantly higher in patients in group 1 (228.75 [142.85; 260.0]) compared to the 2 group (135.25 [100.0; 181.30]) and the 3 group (119.95 [92.75; 144.8]) (p< 0.05). %S among the representatives of the 1group (34.10 [28.9; 52.05]) was significantly lower than the corresponding indicator in the 2 group (55.25 [42.30; 82.55]) and the 3 group (85.0 [92.75; 144.80]) (p<LT; 0.05). The parameter % B showed a positive correlation with the presence of liver steatosis (r = 0.29), while the % S showed a negative correlation with waist circumference (r =-0.32) and presence of pancreatic steatosis (r =-0.26) (p<LT; 0.05).

Conclusion: The study of the HOMA2-IR index showed an increase in the secretory function of β-cells in children with pancreatic steatosis, along with a decrease in cellular sensitivity to insulin. We propose that there are can be different mechanisms of insulin resistance in the case of liver and pancreatic steatosis.

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Objectives and Study: Our aim was to review all the cases with GIT abnormalities requiring management in a non-surgical Level 3 NICU and acute surgical referrals. For medical NICUs with no access to paediatric surgeons on-site, early diagnosis, prompt referrals, appropriate initial management and prompt transfer are paramount in reducing the morbidity and mortality associated with such cases.

Method: We conducted a retrospective study over a 6 year period - Jan 2010 to Dec 2016 to ascertain cases diagnosed with acute surgical GIT abnormalities. Cases were identified from patient electronic notes, imaging and Badger database.

Results:
- 4228 total admissions over the period
- 304 (7%) had GIT abnormalities.
- 55.2% (168/304) of the babies were diagnosed at 24-30 weeks, 22.4% (68/304) were between 30-36 weeks and 22.4% (68/304) were > 37 weeks.
- Birth Weight was < 1 kg in 43% (131/304) of cases, while 31% (94/304) were 1-2 kg and 26% (79/304) were >2 kg; 18% (57/304) were growth restricted.

The GIT diagnosis were:
- Necrotizing enterocolitis (NEC) (198/304, 65%)
- Atresias (36/304, 12%)
- Obstructions (25/304, 8%)
- Malrotations (19/304, 6%) including: malrotation (2 cases), exomphalos (2 cases), gastroschisis (9 cases) and congenital diaphragmatic hernia (CDH) - 6 cases
- Perforations (22/304, 7%) and
- Others (1 of intestinal duplication, 1 of liver abscess and 2 of eventration).

Atresias were made up of:
- Oesophageal atresia (OA) (13/36),
- Duodenal atresia (9/36)
- Intestinal atresia (7/36),
- Imperforate anus (7/36, 1 with rectocutaneous fistula and 1 with rectovulvar fistula).

Intestinal obstruction
- 25 babies who were transferred out, in 2 cases volvulus was also identified.
- 4 cases Hirschsprung Disease were diagnosed.

Antenatal & Postnatal diagnosis:
- Antenatal: 8% of babies (27/304)
- Postnatal: 91% (277/304), of which 26% (71/277) were identified on Day (D) 1, 35% (98/277) during D 2 - D 10 and the rest of the patients (108/277, 39%) between D 11-135.

Transfers:
- 64% (195/304) of babies were transferred to a surgical unit,
- 36% (109/304) babies were managed on the unit, most (104) for medical NEC, 1 for suspected intestinal obstruction, 1 for left diaphragmatic eversion, 1 baby died before transfer (CDH) and 2 babies had withdrawal of care (Trisomy 18 + OA; 26 weeks with spontaneous intestinal perforation with dysmorphic features and pulmonary hypoplasia).
- Out of the babies who were transferred to a surgical unit 64% (124/195) required surgery and 36%
(71/195) were conservatively managed.
- 61% (186/304) of babies required intubation and ventilation at birth.

**Mortality:** Of 10% (30/304): NEC (19 cases - 10 after withdrawal of care), CDH (2 cases), Staphylococcus sepsis (1 case), OA and dextrocardia (1 case) and in 6 cases after withdrawal of care.

**Conclusion:** GIT abnormalities formed a small number of admissions over the 6 year period, the greater part were NEC cases. Majority of cases were diagnosed postnatally, after Day 10 of life, and were more commonly in preterm babies. Mortality rate in this cohort was high, but none due to delayed transfer issues, rather majority was after withdrawal of care, which raised complex ethical issues.

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**Objective:** To describe the clinical presentation and treatment of a patient with congenital agastria.

**Methods:** A case report of a patient with congenital agastria who received care at Instituto Nacional de Pediatría, México.

**Results:** A 2-month-old Mexican female with a history of prematurity of 34 weeks and necrotizing enterocolitis presented with progressive vomiting and oral feeding intolerance. She had been managed with prokinetics and a cow’s milk protein exclusion diet. Barium upper gastrointestinal (UGI) series showed overdistention of the esophagus, absence of the esophagogastric junction, stomach with a tubular appearance, and delayed gastric emptying (See figure1). Abdominal ultrasonography showed dilatation of the esophagus of 15 mm of diameter, and a stomach volume capacity of 10 ml. Based on the imaging findings, a diagnosis of probable congenital microgastria was made. Continuous infusion of extensive hydrolysate formula was given by nasogastric tube with adequate tolerance and good weight gain. In the following days, upper endoscopy was performed, which showed significant dilatation of the oesophagus and a stomach with atrophic mucosa and no gastric folds; the esophagogastric junction was not evident. Biopsies where taken from what appeared to be the stomach, however, these were reported as squamous epithelium, which suggested a diagnosis of congenital agastria. Echocardiogram, transfontanellar and renal ultrasound were normal. Hemogram and blood smear were within normal limits. A Hunt- Lawrence procedure, which is a gastrojejunal anastomosis was performed without surgical complications such as infection and pulmonary atelectasis. Oral feeding was reinitiated with good tolerance and weight gain.
Conclusions: Congenital microgastria (CM) is a rare but well documented anomaly, however, to our knowledge there is only one case report of congenital agastria (CA) in the medical literature. CM and CA have been described as a constellation of embryological anomalies of the normal foregut development. These anomalies are characterized by a small, tubular stomach in a midsagittal position, with minimal reservoir and dilated esophagus in barium contrast study. We suggest to perform upper endoscopy with biopsies in these patients in order to confirm the diagnosis. CA clinically presents with gastroesophageal reflux, vomiting, aspiration, malnutrition, failure to thrive, and in severe cases, death. In the case of our patient, vomiting was the only symptom. This embryological anomaly is usually associated with VACTERL syndrome (vertebral anomalies, imperforate anus, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal and limb anomalies), malrotation, cardiorespiratory failure, and asplenia. Our patient did not show any other anomalies. Most current procedures involve the creation of some kind of jejunal pouch. The Hunt-Lawrence pouch procedure is a good option for the treatment of this condition as gain weight and dumping control is achieved.

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Upper gastrointestinal symptoms prevalence and severity among chronic kidney disease children

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Objectives and study: Gastrointestinal disorders are common (7.4% to 74%) in chronic kidney disease (CKD) patients, the prevalence and severity of these symptoms may differ in pre-dialysis and on dialysis patients. Most of available data belongs to adult studies with few ones conducted in children. This cross sectional observational study was conducted to evaluate upper GI symptoms prevalence and severity among predialysis grade III and IV CKD children versus those on hemodialysis.

Methods: A 125 patients with CKD stage III-V were screened for persistent or recurrent upper GI symptoms for at least 3 months. One hundred eight (86.4%) children reported upper GI symptoms; 33 patients were excluded [refusal to participate (4); confusing associated lower GI symptoms (16); other associated disorders (13)]. Remaining 75 CKD children (male/female = 45/30; age = 10.6±2.78ys) were divided into pre-dialysis (PD) group 33(42%); and on hemodialysis (HD) group 42(56%) patients. Furthermore HD group was subdivided into efficient dialysis group 28 (37.3%) and inefficient dialysis group 14 (18.7%) children according to dialysis efficacy equation. Clinico-epidemiologic data including CKD grade; presence of alarming GI symptoms and signs; symptoms severity and frequency scoring were reported.

Results: Abdominal pain was the most common symptom (93.3%) followed by nausea and vomiting (72%), while the least reported symptom was dysphagia (10.7%). The most bothersome symptom(s) was (were) pain alone; vomiting alone; pain and vomiting; pain and upper GI bleeding; and lastly pain, vomiting and upper GI bleeding reported in [13 (17.3%); 5 (6.7%); 41 (54.6%);8 (10.7%) ; 8 (10.7%) respectively]. The symptoms severity as measured on 5-points scale was reported as 2-mild; 3- moderate; 4- severe; 5-very severe in 2 (2.7%); 31 (41.3%); 32 (42.7%); and 10 (13.3%) patients, respectively. While the symptoms frequency was reported as 2- ≤ 2 times /week; in 7 (9.3%) patients; 3- ≥ 3 times /week, not daily: in 27 (36%) patients; 4- daily, intermittent: in 33(44%) patients; and 5- daily, almost continuous: in 8 (10.7%) patients. Presence of any of alarming GI symptoms was reported in 23 (30.6%) patients. Severe abdominal pain was the most common reported alarming symptom 22 (29.3%) followed by GI bleeding; persistent vomiting; and dysphagia in 16 (21.3%); 14 (18.6%); and 8 (10.7%) patients respectively. Heart burn and belching were significantly more reported among HD group (p=0.001 & 0.022 respectively); also alarming symptoms presence was reported in 18 (42.8%) HD patients versus 5 (15.1%) PD patients; (p=0.017) respectively. Children on HD reported a significantly higher average symptoms frequency and severity than PD children (p = 0.002 & 0.047 respectively). Patients on Inefficient hemodialysis had significantly reported alarming symptoms more frequent than efficient dialysis group [10 (71.4%) vs. 8 (28.5%); p=0.004] as well as higher average symptoms frequency (p= 0.04).

Conclusion: Upper GI symptoms are very common in CKD children; alarming GI symptoms are present in almost one third of these patients. Upper GI symptoms tend to be more severe among HD patients particularly those with inefficient dialysis.

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Significant reduction of catheter-related infections in pediatric intestinal failure patients after protocol-based central line care including Taurolidine locks

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Aim: To analyze catheter-related blood-stream infections (CRBSI) in pediatric intestinal failure (IF) patients during 2003-2017, with emphasis on temporal changes and risk factors.

Methods and patients: We identified all IF patients treated by our tertiary institution multidisciplinary IF team since 2003 (with full electronic patient records available), and collected data relating to the causes of IF and details of intestinal anatomy post-surgery. We noted the exact duration of PN, clinical infection history and blood microbial cultures since referral to us. CRBSI was defined by signs of clinical infection coinciding with positive bacterial blood culture. We established the present multidisciplinary team in 2009. Our CVC line care policy has included use of only industrial 3-chamber PN bags since 2011, and universal Taurolidine locks since 2013.

Results: A total of 70 pediatric onset IF patients were included here (boys n=41). Their median PN duration was 10.7 months (range 1 month - 25 years). Median age at referral to our unit was 2.4 months (0-12 years) and follow-up 4.4 years (0-25). The patients were diagnosed with Short bowel syndrome (n=53), Primary intestinal dysmotility disorders (n=11) and Congenital intestinalopathies (n=6). Median percentage of remaining SB proportion among SBS patients was 26% (interquartile range 19.5-46%), and 30/53 (57%) had intact ileocecal valve. Culture proven blood stream infections occurred in 1.01/1000 PN days (95%CI 0.80-1.2) in the entire cohort. CRBSIs decreased from 1.4 to 0.6/1000 PN days (P=0.0003) comparing the eras 2003-2012 and 2013-2017. CRBSIs were most frequent in SBS patients (1.4/1000 d, 95%CI 1.1-1.9) compared to other patients (0.5/1000 d, 95%CI 0.3-0.7), p< 0.0001. Three individuals experienced 24 out of the 74 CRBSIs (32%), all of whom had SBS. In fact, among those with more than two CRBSIs (n=13), SBS was the most common diagnosis (n=10), and ICV was absent in 9/13 (70%). Causative bacteria included mainly staphylococcus epidermidis, staphylococcus aureus and enterococci. Fungal infections were rare, see Table 1.

<table>
<thead>
<tr>
<th>Staphylococcus epidermidis</th>
<th>Enterococci</th>
<th>Staphylococcus aureus</th>
<th>E. Coli</th>
<th>Enterobacteria</th>
<th>Candida</th>
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<td>18</td>
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Conclusions: Certain individuals seem to possess an increased risk for recurrent line infections. Still, a protocol-based CVC infection control program (including universal taurolidine locks) associates with lower CRBSI rates in the entire cohort of pediatric IF patients. Patients with short bowel syndrome have higher risk for CRBSI's, even when dysmotility and intestinalopathy patients have longer total duration of PN.

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The natural history of eosinophilic esophagitis in a tertiary hospital in the United Kingdom

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Objectives and Study: Eosinophilic Esophagitis (EoE) is a chronic, immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, defined as at least 15 eosinophils per high-power field (HPF). Untreated EoE is usually associated with persistent symptoms and can lead to esophageal remodeling resulting in stricture formation and functional abnormalities.

Method: We have conducted a retrospective review of patients in our Tertiary Institution diagnosed with Eosinophilic Esophagitis between 2007-2017, whose treatment followed the ESPGHAN guidelines. Patients with Inflammatory Bowel Disease, Coeliac disease and Eosinophilic Gastrointestinal Disease beyond the esophagus were excluded. Patient demographics, presenting symptoms, response to therapy and long term-outcomes were analysed. At least five biopsies were obtained from different areas of the esophagus.

Results: Twenty six patients fulfilled the inclusion criteria; 2/26 had congenital trachea-esophageal fistula. 17/26 (65%) patients were male, 9 female. 61% had atopic history. The mean age at presentation was 6.5 years. Eighteen patients presented with severe symptoms, such as solid food dysphagia, food impaction, food refusal or failure to thrive. Eight children had mild symptoms, including retrosternal or abdominal pain, reflux-like symptoms and vomiting. Half of the patients had macroscopic changes of the esophageal mucosa including furrows, corrugated esophagus, white spots, erosions, trachealization and strictures. Histological findings were compatible with basal zone hyperplasia (95%), intracellular oedema and scattered intraepithelial mononuclear cells. Eosinophilic density ranged from 15 to 100/HPF and in some cases eosinophilic abscess formation was observed. 11/26 patients were started on a Proton Pump Inhibitor (PPI) and 7/11 (64%) of them responded well giving the phenotype of PPI-Responsive Eosinophilia. Of note, 15/26 patients had already been started on PPI before their first endoscopic assessment, without response and they were hence started on topical steroids or exclusion diet or combination of both. Empiric elimination diet was used in 6 and targeted diet in 5 cases, based on history of food triggers or results of specific Immunoglobulin E. Symptoms improved in 42% of non PPI-responsive patients, after first-line treatment, not accurately correlating with histologic disease activity. In those where the symptoms persisted, the treatment was escalated. Five patients had more than one course of topical steroids. Three patients developed strictures and esophageal narrowing requiring one or more dilatations, but no correlation between eosinophilic density and this phenotype was found.

Conclusion: Our results are in keeping with the literature. Eosinophilic Esophagitis is a chronic, relapsing disease which requires prolonged therapy in most patients. However, just under one third of patients (7/26) responded to PPI therapy. We could not establish a correlation between severity of symptoms and histological features and long term follow up is hence advisable.
Insights into paediatric autoimmune gastritis: is there a role for Helicobacter pylori infection?

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Objectives and Study: Autoimmune gastritis (AIG) is a rare inflammatory condition of the stomach, a multifaceted disease whose diagnosis should rely on clinical and laboratory suspicious and histopathological confirmation. The primum movens of autoimmunity in AIG is still unknown, and it is unclear whether Helicobacter pylori (HP) may be a trigger. The main objective was to characterize clinical, laboratory, and histological profile of pediatric autoimmune gastritis in a cohort of children followed at our institution.

Methods: Only children with positive anti-parietal cell and/or intrinsic factor antibody were included.

Results: We report a case-series concerning 18 patients (11 girls and 7 boys) with a mean age at presentation of 11.3 ± 5.2 years. In the majority (14/18) the diagnosis was suggested during the investigation of IDA [Hemoglobin (Hb) < 2 SD for age and sex and serum ferritin < 15 ng/mL] with refractoriness to oral iron therapy for at least 6 months. Half of them (9/18) had concomitant diseases: autoimmune thyroiditis (2), type 1 diabetes (2), both autoimmune thyroiditis and type 1 diabetes (2); and nephrotic syndrome in 2; celiac disease in 1.

Main laboratorial evaluation on admission included: Hb: 9.65 g/dL (6-15.4); serum ferritin: 5 ng/mL (1-108); serum gastrin: 535pg/mL (15,1-2247); low pepsinogen I/pepsinogen II ratio in 6/13 patients. Only 1 patient had positive Intrinsic Factor Antibody.

Endoscopy findings included gastric fold softening and/or visibility of vascular pattern in 11/15 patients. Histological evaluation showed predominantly corpus and/or fundus atrophic gastritis with lymphocytic infiltration in 10 and intestinal metaplasia in 3. Duodenal histology revealed villous atrophy in 2 patients. Ten biopsies were positive for HP (7 only Giemsa staining positive; 3 culture and/or PCR positive). Eradication therapy was performed in all patients but one.

Conclusion: Although pernicious anemia is considered the classic hematological presentation of AIG, we highlight IDA as a precocious manifestation of this gastric condition in children, which may otherwise be asymptomatic. Furthermore, AIG is associated with autoimmune diseases, namely autoimmune thyroid diseases and type 1 diabetes mellitus. Concerning HP infection, we had a percentage of positivity comparable with other studies, reporting about 30-65% of infection depending on the method utilized. Our small cohort and its retrospective nature do not allow to draw conclusions regarding the role of HP as a trigger for the development of the autoimmune process in the gastric mucosa.

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Objectives and Study: Asthma is one of the most common diseases in Russia. Currently, the investigation of microbiota influence on asthma development is a topical issue. The aim of this study was to identify composition of intestinal microbiota of children with bronchial asthma in Saint-Petersburg.

Method: In the study were included 32 school-aged children with moderate persistent asthma, who were under drug-free remission (3-6 month) of underlying disease and received medium doses of inhaled corticosteroids (IGCs) as basic therapy (delivery method-spacer). Mass-spectrometry of microbial markers to assess gut microbiome was performed.

Results: The state of intestinal microbiota in the examined children was characterized by a decrease in the number of most representatives of normobiota, the absence of certain species of bacteria and the excessive growth of Ruminococcus and streptococcus mutans. It was found the correlation between the number of bacteria of the gut microbiota and spectrum of sensitization: the number of Ruminococcus correlated with the sensitization to casein (r=0.53), weeds (r=0.79) and cereal (r=0.56); Eubacterium/Cl. Coccoides - weeds (r=0.59); Eggerthella lenta - cereals (r=0.52).

Conclusion: School-aged children with moderate persistent asthma are characterized by reduced diversity of the gut microbiota; reduced number of the studied the gut microbiota with the only increased Ruminococcus and Streptococcus mutans (anaerobe); correlation between gut microbiota and the spectrum of sensitization.

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Evaluation of maternal risk factors for necrotizing enterocolitis in premature new born with gestational age under 28 weeks

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Objectives and Study: A number of factors related to the antenatal period may have a significant influence on the development of necrotizing enterocolitis (NEC) in newborns, especially in those born prematurely. The purpose of this study was to investigate the most representative maternal factors that can influence the appearance of NEC.

Method: There were studied over a period of 4 years, 988 newborns with gestational age less than 28 weeks in nine level III maternity centers from Romania. The lot was divided into two categories: with or without NEC.

The maternal factors studied were: chorioamnionitis, diabetes mellitus, eclampsia, intrapartum haemorrhage, hypertension, broken membranes over 48 hours, antenatal corticoids, corticoid cure (complete / incomplete), birth type, place of birth.

In order to identify the maternal risk factors involved in the occurrence of NEC, we used Chi-square (Fisher) statistical test and Wald binomial logistic regression test.

Results: There were 890 newborns without NEC (90.08%) and 98 (9.91%) newborns with NEC.

The NEC subgroup had a higher percentage of cases whose mothers had chorioamnionitis, eclampsia, HTA, intrapartum hemorrhage or broken membranes>18h.

Regarding the antenatal corticosteroids, in both groups exceed neonates who have not received corticosteroid therapy, the highest percentage is the group without NEC (79.43%), but with incomplete cure (53.58%).

Vaginal birth prevailed in both groups, with a higher percentage in the NEC group (71.42%).

Also, the lot with NEC had a higher percentage of cases born outside the center (30.61%), compared to the non-NEC lot.

Following the statistical analysis it was found that there is a statistically significant influence of eclampsia (p = 0.04) and place of birth (p = 0.02) on the occurrence of NEC in premature babies under 28 weeks in this study.

Maternal risk factors for the development of NEC identified by multiple regression for the gestational age≤28 weeks group were in the order of significance: birth outside the center (B = 0.53, p = 0.02), maternal eclampsia (B = -0.99, p = 0.03) and on the 3rd place, at the limit of significance was the absence of antenatal corticosteroids (B = 0.39, p = 0.06).

Conclusion: Investigating the contributing factors to NEC from the antepartum period, it is possible to improve understanding of NEC pathophysiology and determine whether certain maternal risk factors contribute to its development in the premature infants.

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Intercostal muscle pedicle flap to prevent imminent perforation after button battery ingestion

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Objectives and Study: Foreign body ingestions are common in children. In most cases, they do not cause significant complications. However, button battery ingestions may result in fatal aortoesophageal fistula. They have the potential to cause significant morbidity and mortality. The feared complication is hemorrhagic shock, which has been associated with a 100% mortality rate. Literature suggest this can occur up to 4 weeks after ingestion of a button battery.

Methods: We are reporting the case of a girl who required intercostal muscle pedicle flap grafting to separate the aorta from the esophagus after ingestion of a button battery to prevent lethal aortoesophageal fistula formation.

Results: This is a previously healthy 8 year old female who ingested a button battery 3 days prior to presenting with abdominal pain and intermittent vomiting. She was given Pepto-Bismol without improvement. As the family went traveling she admitted to her mother that she may have ingested a battery 3 days prior. She was taken to another institution where an upper endoscopy and removal of the foreign body was performed from the distal esophagus. Significant erosion in the distal esophagus was noted. She was started on Pantoprazole. A Gastrografin swallow study was obtained, which showed a grossly normal esophagus without leaks or stricture. However, due to inherent risk of perforation she was transferred to our institution. Upon arrival a CT Angiogram was performed that showed focal esophageal wall edema of the distal esophagus, in the right lateral position, no discrete mediastinal fluid collections, mild dependent atelectasis bilaterally, and trace right pleural effusion. Given these findings she was taken to the OR by the pediatric surgeon for left thoracotomy, mobilization of descending aorta and esophagus, division of inferior pulmonary ligament, imbrication of damaged lateral esophageal wall with pen rose drain placement, and intercostal muscle pedicle flap to separate the aorta from esophagus. She was subsequently returned to the ICU with a chest tube. Post-op day 3 esophagram revealed considerable irregularity of the wall of the distal third of the esophagus, above the GE junction, with generalized slight narrowing of the lumen but without stricture. On post-op day 3 she was started on a clears diet and advanced to soft diet. She was eventually discharged home. Upon outpatient follow up, she continued on Pantoprazole BID, without dysphagia, vomiting, or pain. A repeat esophagram at 1 month showed minimal residual narrowing of the distal esophagus.

Conclusions: Based on current data there is no predictive factors for aortoesophageal fistula or strictures. Grafting of intercostal muscle between the aorta and esophagus may prevent hemorrhagic shock, cardiovascular collapse, and subsequently death. Diagnostic imaging studies may be beneficial in identifying the few cases who have suspected increased risk of perforation and fistula development.

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Accuracy of the LCT-13910 C/T genotype in detecting a positive hydrogen breath test in children with suspected lactose intolerance: a case-control study

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Objectives and Study: In adults, the LCT-13910 C/T polymorphism is considered a good test to detect the presence of a positive hydrogen breath test (HBT) but few studies are available in children. We performed a case-control study to evaluate the accuracy of the LCT-13910 C/T polymorphism to detect a positive HBT in children and adolescents.

Method: 182 children and adolescents with suspected lactose intolerance were included in the study, 88 with positive HBT (HBT+, cases) and 94 with negative HBT (HBT-, controls). Out of the 182 children, 170 children were Caucasian (Italy), 8 Hispanic (Central and South America), 3 African and 1 Asiatic. Genetic testing for the 13910 C/T polymorphism was performed on cells collected from the oral cavity with a brush.

Results: The sex distribution was similar in HBT+ and HBT- children (p = 0.44, Pearson’s Chi-square test). The median age was higher in HBT+ than in HBT- children (median difference = 0.8, 95%CI 0.5 to 3.5 years, p < 0.001, median regression). The odds ratio of HBT+ in CC+ vs. CC- children was 14.4 (exact 95%CI 4.2 to 76.9, exact p < 0.001, exact univariable logistic regression). The corresponding probability of HBT+ in CC+ children was 0.58 (exact 95%CI 0.49 to 0.65). Age was independently associated with HBT+ (OR = 1.11, 95%CI 1.02 to 1.21 for 1-year increase of age, p = 0.013) but modified only slightly the effect of CC (OR = 12.8, exact 95%CI 3.7 to 68.8, p < 0.001) (exact multivariable logistic regression). The probability of HBT+ in CC+, i.e. the TPR, increased from 0.49 (exact 95%CI 0.37 to 0.60) at 6 years of age (25th percentile of age in the pooled sample) to 0.57 (exact 95%CI 0.48 to 0.65) at 9 years of age (50th percentile) to 0.64 (exact 95%CI 0.54 to 0.73) at 12 years of age (75th percentile). The odds ratio of HBT- in CC- vs. CC+ children was 0.91 (exact 95%CI 0.77 to 0.98). The corresponding probability of HBT- in CC- children, i.e. the TNR, was 0.91 (exact 95%CI 0.77 to 0.98). The probability of HBT- in CC- decreased from 0.93 (exact 95%CI 0.80 to 0.98) at 6 years of age (25th percentile of age in the pooled sample) to 0.91 (exact 95%CI 0.75 to 0.98) at 9 years of age (50th percentile) to 0.87 (exact 95%CI 0.68 to 0.97) at 12 years of age (75th percentile).

As determined by clinical challenge, 21 out of 94 (22%) breath tests were falsely negative and 9 out of 88 (10%) breath tests were falsely positive. Figure 1 shows the flow of patients through the study.
Conclusion: In the present case-control study, CC had a true positive rate of 58% (95% CI 49 to 65%) and a true negative rate of 91% (95% CI 77 to 98%) for detecting HBT. It appears therefore that 13910 C/T genotyping may be useful to rule out HBT+ in children. Further cross-sectional studies taking into account the prevalence of HBT are needed to test whether these findings are relevant in clinical practice.

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Primary lactose intolerance (PLI) is caused by a genetically programmed and progressive loss of lactase expression. PLI is the ancestral variant, while lactase persistence is caused by 2 polymorphisms: the dominant C/T13910 and G/A22018. Homozygotes (CC or GG) have undetectable lactase levels. In clinical practice only half of people with PLI have symptoms. Recent studies have linked lactase persistence with higher anthropometric indices. Still, the relationship between lactase persistence and obesity and metabolic abnormalities is yet to be defined.

Objectives and Study: To investigate whether genetic predisposition to PLI is associated with typical symptoms. To assess whether genetic predisposition to PLI has an influence on children's anthropometric and metabolic profile.

Method: We conducted a prospective study, recruiting consecutive children evaluated in our unit in May-August 2016. We enrolled 87 children aged 6-17 years (mean age 10.64±3.51 years), 45 (51.72%) girls. Subjects were asked to complete an analogue visual scale of symptoms. We measured weight, height, blood pressure (BP) and calculated BMI. Metabolic markers included blood glucose, triglycerides (TG) and HDL cholesterol (HDLc) levels. We used strip genotyping to identify genetic predisposition to IPL. According to the results, we grouped our study population into lactose tolerant (LT, n = 45) and genetically predisposed to lactose intolerance (LiT, n = 42).

Results: 45 (51.7%) subjects had a CC genotype. 30 (34.5%) subjects had a GG genotype. 15 (17.4%) children were homozygous for both. Our results were consistent with Hardy-Weinberg equilibrium. 5 children did not complete the scale of symptoms. 75.6% of children (62/82) showed no or mild symptoms. We found similar symptom profiles in LT and LiT children (p = 0.25). We found no differences in weight (42.9±16.94 vs 39.07±17.41 kg, p = 0.37), height (148.67±18.06 vs 144.37±18.38 kg, p = 0.27), BMI (19±5.08 vs 17.99±4.65 kg/m², p = 0.44) and BP (systolic: 99.8±5.49 vs 98.43±6.87 mmHg, p = 0.33; diastolic: 67.74±10.47 vs 68.25±8.51 mmHg, p = 0.85) across study groups. Glucose (85.47±13.5 vs 87±9.3 mg/dl, p = 0.46), TG (79(52.39) vs 63.5(63.86) mmol/l, p = 0.39) and HDLc (45(21.75) vs 43(13) mmol/l, p = 0.19) levels were similar in LT and LiT children.

Conclusion: Genetic predisposition to IPL was not associated with typical symptoms. Genetic predisposition to IPL did not influence children's anthropometric and metabolic profile.

This work has been supported by an internal grant of "Victor Babes" University of Medicine and Pharmacy, PII-C4-TC-2016-08
Gastrointestinal and associated manifestations in paediatric patients with food allergies - A retrospective study

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Objectives and Study: Among the most common reasons for addressing the paediatric gastroenterologist are food allergies, especially in infants and young children. Cow's milk protein and hen's egg protein represent the most important triggers of allergies in the paediatric population. The rise in incidence and the diversity of this pathology, alongside the difficulty of following an elimination diet are the main grounds on which food allergies are becoming a growing health care concern. In the present study we assessed the clinical manifestations that occurred in children admitted to our ward under this suspicion.

Method: In this retrospective study were included patients admitted to our ward between January 2013- July 2017. The inclusion criteria was a diagnosis of food allergy, based on medical history, clinical evaluation, IgE antibodies or response to elimination diet. Data regarding age, sex, atopic comorbidities, gastrointestinal (GI) symptoms, blood tests (immunoglobulin E- IgE), stool tests, atopic family history and diet were recorded.

Results: Data from 95 children were included in the analysis, with an age range between 6 weeks to 9 years. Seventy percent of the children in the study presented GI symptoms at admittance. Among these, diarrhea or bloody stools were twice as frequent as reflux. The proportion of patients with an increased value of IgE was comparable to literature data. In the cow's milk protein allergy group, 20% associated dermatitis, bloody stools and hyper IgE and 20% presented respiratory symptoms. At follow-up, all patients under 1 year of age responded positively to the elimination diet. Almost half of the patients had a positive family history for allergies. In older children, hen's egg protein allergy and peanut allergy are still present at the challenge test, despite the elimination diet.

Conclusion: In our cohort, cow's milk protein allergy was commonly associated with GI symptoms like diarrhea and bloody stools. In infants, symptoms resolved following elimination of dietary cow's milk protein. Regarding older children, in which hen's protein allergy and peanut allergy were the most common, the strict diet is impossible to achieve. Due to their involvement in social activities, the contact with the allergens cannot be restrained completely, so patients are easily faced with relapses. regarding extended investigations, the significance of more than two target organs affected (skin, GI tract and respiratory tract) and a correlation to the severity of the disease are yet to be investigated.

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Antibiotic use in cirrhotic children with upper gastrointestinal bleeding

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Objectives and Study: Current AASLD and ASGE guidelines recommend antibiotic prophylaxis in all cirrhotic patients presented with upper gastrointestinal bleeding (UGIB). This practice has shown to reduce the incidence of bacteremia and improve survivals in adult cirrhotic patients with UGIB. However, the use of antibiotic prophylaxis in cirrhotic children with UGIB is not well established and varies between institutions. The aims of this study were to investigate current practice of using antibiotics in cirrhotic children with UGIB and to evaluate its impact on the patient outcomes.

Methods: This was a retrospective study using the Pediatric Health Information System (PHIS) database. The PHIS network includes 44 of the largest children’s hospitals in the United States. Cirrhotic children aged 18 years or younger with UGIB admitted between 2007 and 2016 were identified based on ICD-9 code. Data were collected for baseline patient characteristics, hospitalizations, primary diagnosis, complications of cirrhosis, bacteremia, blood products given, medications including antibiotics, proton pump inhibitors (PPIs), and octreotide. Patients with no endoscopy performed during the admission were excluded. Groups of patients with and without antibiotic use were compared using chi-square test or Fisher’s exact test for categorical variables, and using t-test for continuous variables.

Results: Among 152 cirrhotic children admitted during the study period, 44 patients with UGIB (23 female, 53%) were eligible for data analysis. The median patient age was 6 years (interquartile range [IQR]=11). The majority of the patients were white (n=36, 82%). The most common primary diagnosis was biliary atresia (n=21, 48%), alpha-1 antitrypsin deficiency (n=5, 11%), and autoimmune hepatitis (n=2, 5%). Etiology of UGIB included esophageal varices (n=37, 84%), non-variceal bleeding (n=4, 9%), and both (n=3, 7%). Most patients were started on PPIs (n=35, 80%) on admission, but only 20 (45%) received octreotide in addition to PPIs. Thirty patients (68%) were given intravenous antibiotics, and all were started within 48 hours after admission. The median duration of antibiotic use was 3 days (IQR=6). Among children receiving antibiotics, 4 (13%) had bacteremia, versus 26 (87%) in those with no antibiotics (p=0.6). The median hospital stay was 7 days (IQR=9) in children with antibiotic use versus 5 days (IQR=16) in those with no antibiotics (p=0.05). However, the rate of re-admission within 30 days after discharge was lower in patients receiving antibiotics (7% versus 21%, p=0.3).

Conclusions: A significant proportion (68%) of cirrhotic children with UGIB were given antibiotics timely after admission. The use of antibiotics appeared to prevent bacteremia and reduce the re-admission rate. A multicenter, prospective study is warranted to further investigate the association between the use of prophylactic antibiotics and outcomes of infectious complications, hospitalization characteristics, and mortality in cirrhotic children with UGIB.

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GASTROENTEROLOGY - Gastroenterology other

G-P-187

Fecal calprotectin and eosinophil-derived neurotoxin in healthy children aged 4 to 12 years

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Objectives and Study: We have previously reported that young infants have higher concentrations of fecal Calprotectin (fCP) and Eosinophil-Derived Neurotoxin (fEDN) compared to adults. The highest concentrations for both biomarkers were found in infants less than 4 years of age. There was also a large variation in fCP and fEDN concentrations between individual children in the 0 to 4 years age group, which stabilized from 4 years of age onwards. The objective of the current study was to investigate fCP and fEDN levels in healthy children 4 to 12 years of age.

Method: Prospective study including 153 healthy children, 4 to 12 years old, from the general population. Fecal samples (n=153) were collected, sent to the laboratory no later than 7 days after collection and stored at -20°C until analysis. The extraction procedure was performed with the Faecal sample preparation kit (Roche Diagnostics). Fecal CP and fEDN levels in the fecal samples were measured by EliA Calprotectin 2 and an EDN research assay developed on the ImmunoCAP platform, respectively (Thermo Fisher Scientific).

Results: The median (50th percentile) of fCP and fEDN concentrations in the 153 children were 20.31 mg/kg and 0.3 mg/kg respectively. The 95th Percentile of fCP and fEDN concentrations were 104.85 mg/kg and 2.01 mg/kg. We did not find a statistically significant association between the median fCP concentration and age (p=0.31) or gender (p=0.97), or for the median fEDN concentration and age (p=0.08) or gender (p=0.059). However we found a statistically significant association between the 95th percentile of fCP and fEDN concentrations with age (p<0.001), and this association was stronger at younger ages and decreased at around 80 months of age. We developed a nomogram showing that the lower 95th percentile of fCP and fEDN concentrations were 108.5 and 1.7 mg/kg, respectively, in the age group 4 to ≤6 years, and 66.2 and 1.1 mg/kg, respectively, in the age group >6 to 12 years. Although the median concentrations for fCP were lower than the 50 mg/kg cutoff value proposed for adults, there was a percentage (21%) of children with fCP concentrations above 50 mg/kg. Therefore, the 95th percentiles of fCP concentrations for the age range of 4 to 12 years were higher than the cutoff value for adults. However, in agreement with our previous study, the fCP concentrations were lower, and showed less variability, in the age group of 4 to 12 years compared to the fCP concentrations in children below the age of 4 years (JPGN 2017 Oct;65(4):394-398).

Conclusion: Based on the results and a developed nomogram, two different age groups for evaluation of fCP and fEDN in children aged 4 to 12 years are suggested: from 4 to ≤6 years, and from >6 to 12 years. We also suggest reference values for fCP and fEDN representing the lower value of the 95th percentile for each age group: 108.5 and 1.7 mg/kg, respectively, in the age group 4 to ≤6 years, and 66.2 and 1.1 mg/kg, respectively, in the age group >6 to 12 years. For fCP, the suggested reference values are higher than the 50 mg/kg cutoff value proposed for adults.

Disclosure of interest: Helena Ekoff and Niclas Rydell are employed at Thermo Fisher Scientific. There are no conflicts of interest for the remaining authors.

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Multicenter, prospective study on clinical implication and sonographic evolution of enlarged abdominal lymph nodes in a cohort of pediatric patients

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Objectives and Study: The current use of high-frequency transducers for sonographic evaluation of the abdomen in children has increased the detection of enlarged abdominal lymph nodes (EALNs). The scientific evidence about the clinical significance of this finding is not univocal. The main purpose of the present study is to evaluate the clinical contest and the evolution of EALNs detected by sonography in children with and without abdominal pain. Secondary purposes are to assess the association between the presence and size of EALNs and possible acute or chronic diseases, and to evaluate the correlation with the main blood inflammatory markers.

Method: Every patient diagnosed with enlarged abdominal lymph nodes (≥1 nodes with maximum diameter ≥10 mm) at the involved Centers was enrolled in the study from September 2016 to June 2017. The presence of EALNs was registered and a new abdomen ultrasound was performed after 3 and 6 months (T1 and T2). The number of lymph nodes, their diameters, localization, shape, and architecture were accurately recorded along with clinical and laboratory data.

Results: 50 children with EALNs were enrolled in the study. Indications for ultrasound study were: 24/58 (41.4%) recurrent abdominal pain (RAP), 6/58 (10.3%) follow-up of Crohn's disease (CD), 9/58 (15.5%) follow-up of ulcerative colitis (UC), 9/58 (15.5%) rectal bleeding, 7/58 (12.1%) acute colitis, 2/58 (3.4%) cystic fibrosis (CF), and 1 (1.7%) autoimmune hepatitis (AH). At T2 the hyperplastic abdominal lymph nodes were: 20/50 reduced in size (40%), 15/50 unchanged by number and size (30%), 8/50 (16%) completely regressed, and 7/50 (14%) increased in size. Among the 24 patients with RAP, at enrollment 12 had positive inflammatory indices and 12 negative inflammatory indices. At T2 the mean maximum diameter of the lymph nodes was 14.4 mm in patients with positive inflammatory indices and 10.8 mm in patients with negative inflammatory indices (p < 0.05).

Conclusion: The clinical significance of EALNs is not univocal. In more than a half of the patients they decrease in size or normalize within 6 months. The decrease of their diameter is higher in children with negative inflammatory markers compared to patients with positive inflammatory markers. A longer follow-up may be useful to better define their evolution.

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Objectives and Study: Physicians are encouraged to include patients in medical shared decision making (SDM) as a cost-effective enterprise to improve patient satisfaction and quality of care. The “3 Good Questions” program was developed by the Dutch Child and Hospital Foundation with the aim to elicit and organise the information provided during patient-physician consultations and has been showed to benefit SDM in adult medicine. The aim of this study was to evaluate the effect of this program on SDM in paediatric medicine.

Method: Children aged 10-18 years attending the paediatric outpatient clinics of four hospitals in the Netherlands were invited to participate in the survey. Children were assigned to either the intervention group, receiving the “3 Good Questions” (i.e. ‘This is what I feel, what is it?’; ‘What can we do about it?’ and ‘What does this mean for me now and later?’) prior to their visit, or the control group, receiving no additional information prior to their visit. After their appointment, children were handed out a Dutch-written questionnaire containing questions regarding their attitudes towards the consultation and, if applicable, towards the “3 Good Questions” program. Frequency distributions and descriptive statistics were computed for survey questions and χ² test was used to test for differences between intervention and control groups.

Results: In total, 114 and 169 children in the intervention and control group (63% vs 61% female, mean age 13.8 ± 2.47 vs 13.3 ± 2.43 years, p = NS), respectively, completed the questionnaire. Fifty children (48%) receiving the “3 Good Questions” were informed about and read the questions prior to their appointment, of whom seventeen (34%) indicated that they prepared their appointment differently. Only nine children (18%) posed the questions during their appointment. The “3 Good Questions” were considered to be helpful to get information and to discuss treatment options with the healthcare professional by respectively 42% and 40% of children in the intervention group. Compared to the control group, children receiving the “3 Good Questions” reported to be more involved in SDM (p = 0.03, 95% CI -0.140, -0.002) and were more often scheduled for a follow-up appointment (p = 0.03, 95% CI -0.099, -0.003). The majority of children (68%) reported that they would recommend the “3 Good Questions” to other children.

Conclusion: This study shows that the “3 Good Questions” program can improve SDM in paediatric medicine. Since only a small cohort of paediatric patients used the “3 Good Questions” program in this study, it is necessary to further explore the implementation of the “3 Good Questions” program for SDM in different areas of paediatric medicine.

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Histopathological parameters on esophageal specimens from childhood are useful to differentiate eosinophilic esophagitis and other diseases requiring upper digestive endoscopies

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Objectives and Study: Eosinophilic esophagitis (EoE) is a chronic clinical-pathological disorder immune/antigen-mediated, characterized by symptoms of esophageal dysfunction and histopathological alterations inflammatory with at least 15 eosinophils (EOS) per high-power field (EOS/hpf). This histopathological finding is usually accompanied by other morphological changes in the esophageal mucosa: cell hyperplasia of the basal layer, papillary elongation, dilation of the intercellular space and presence of microabscesses.

EOS number on esophageal biopsies specimens is crucial for EoE, however, the value of other histology features remain unclear.

The study aims are to describe these histopathological findings from pediatric and adolescent patients with EoE and to compare them with patients with other diseases leading to upper gastrointestinal endoscopy (UGIE) to analyze their utility on the EoE diagnosis.

Method: 17 patients with diagnosis of EoE and 17 patients with other gastrointestinal symptoms who underwent UGIE follow-up at the Clinical Hospital of the Federal University of Uberlândia- Brazil, matched by gender and age, were invited to participate in the study after approval by Ethics Committee, between January 2015 and January 2016.

During the UGIE exam, which was performed to monitor patients with EoE and/or to diagnose investigation for other gastrointestinal diseases, four fragments were collected for histological analysis (two in the middle and two in the upper third of the esophagus) from all patients. The slides were analyzed by two pathologists independently in order to determine the following histopathological aspects, based on the number of EOS and their predominant location, presence and intensity of papillary elongation, presence and intensity of basal cell hyperplasia, presence and intensity of dilated intercellular spaces (spongiosis).

Immunohistochemical analysis with the anti-human CD1a monoclonal antibody was done to verify if there was an increase of antigen-presenting cell, by Cd1a expression above the basal and parabasal layers.

Results: In each group there were 58.8% male and 41.2% female patients, with average age of 11 in EoE group and 10 in the other. The means of EOS found were 157.88 EOS/hpf in the group of EoE and 1.29 EOS/hpf in the other group.

The presence of elongation of lamina propria papillae and the basal cell hyperplasia in the EoE group was observed in all participants but was not verified in the other group. Microabscesses were found in 52.9% patients with EoE and none in the patients without EoE. Spongiosis was found in all patients in the EoE group, and 76.4% of the patients presented significant dilated intercellular space. Among patients of the other group, 29.4% presented the alteration. The increase in Cd1a expression above the basal and parabasal layers was found in 58.8% of patients with EoE, and was not observed in any other patients.

Conclusion: All the morphological and immunohistochemical findings described above presented a statistically significant difference between the two groups.

The histopathological and immunochemical aspects proved to be useful resources in addition to EOS number for EoE diagnosis.

These parameters can help in the diagnosis and follow-up of these patients.

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Body Image: self-perception and parental perception and the relationship with sociodemographic and anthropometric factors

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Objectives and Study: To evaluate if there is distortion of parental perception and self-perception of the body image of children and adolescents with excess weight between 7 and 12 years of age, attending the pediatric outpatient clinic of an European tertiary Hospital, and comparing them with sociodemographic factors and anthropometric.

Method: A cross-sectional study was conducted, in a convenience sample, which included children between 7 and 12 years attending the outpatient tertiary Hospital, represented by one of their parents. Parents’ perception was assessed in 286 cases and the Self-perception of children/adolescents was assessed in 88, through silhouettes of Idalina Kakeshita Scale. Parents were asked about sociodemographic factors; was taken anthropometric assessment of all elements of the sample. The statistical analysis used test t-student, chi-square, and ANOVA.

Results: Of the 286 children/adolescents, 38.8% had obesity and pre-obesity 15.4%. Parents on average underestimate the Body Mass Index (BMI) of children in a picture of the scale (-0.63 ± 1.50) and the greater age of son, the greater distortion (p = 0.004). On average, parents are dissatisfied with the nutritional status of the children, wishing they were a figure below the current state (-1.12 ± 2.15). The satisfaction is related to the nutritional status of parents, the higher BMI, higher dissatisfaction (p <0.001) and the employment situation of parents - inactive (p = 0.038). The distortion of descendant is influenced by his nutritional status, and was higher in obese children. As for dissatisfaction with body image, children want to be two figures below the picture of the current state (-2.17 ± 2.73). The dissatisfaction of descendant was significantly higher in parents and children with higher BMI (p &LT; 0.001).

Conclusion: Parents underestimate and are dissatisfied with the nutritional status of their children. Children do not have distortion statistically significant, but reveal dissatisfaction with body image.
Outcome of percutaneous endoscopic gastrostomy in children with neurological impairment at Red Cross War Memorial Children’s Hospital, South Africa

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Objectives and Study: Many children with neurological impairment (NI) require a percutaneous endoscopic gastrostomy (PEG) for feeding. There have been reports of increased PEG-associated morbidity and mortality in these children. The aim of this study was to evaluate the outcome and complications following PEG insertion in children with NI.

Method: A retrospective record review was conducted of all children < 13 years with NI who had a PEG placed from January 2011 to December 2015 at Red Cross War Memorial Children’s Hospital (RCWMCH), a South African paediatric tertiary referral hospital. Outcomes and major and minor complications were assessed by Kaplan-Meier survival analysis.

Results: One hundred and ten children (59.1% [n=65] male; median age 2.6 years [Interquartile range, IQR 0.9-6.4 years]) had a PEG inserted during the study period. All children had neurological impairment and the majority (103, 94%) had one or more comorbid conditions with 84 (76.4%) having more than two.

Most children (86/110, 78.2%) had the PEG changed to a gastrostomy at a median time period of 190 days post-insertion (IQR 140-232), 5 (4.6%) PEGs were removed electively, 7 (6.4%) children died and 12 (10.9%) were lost to follow up. No deaths were related either to PEG insertion or change to gastrostomy.

Eleven (10%) children experienced thirteen major complications, one child with HIV and severe immunosuppression experiencing four. There was one perforated transverse colon, 4 major local sepsis episodes, 7 PEGs dislodged requiring reinsertion and 1 buried bumper. Overall 4/11 (36%) children experienced major complications in the first week after PEG insertion; 10/11 (91%) within two months of insertion; and one had a buried bumper at 213 days. In Cox regression analysis, the only risk factor for experiencing a major complication was the number of attempts made to insert the PEG (Hazard ratio [HR] 3.21 [95% CI, 1.15-8.94])

Six (5.5%) children subsequently needed Nissen fundoplication for worsening gastro-oesophageal reflux disease. There were 16 (14.5%) children who experienced minor local complications including minor local sepsis treated with oral antibiotics (3), temporary obstruction of the PEG (5) and the PEG breaking and leaking prior to change to gastrostomy (8). Only one child experienced both a major and a minor complication.

Conclusion: Although PEG insertion is generally a safe procedure, major complications may occur in 10% of neurologically impaired children. There were no deaths related either to PEG insertion or change to gastrostomy. Complication rates experienced were similar to those reported in the literature and suggest that children with NI do not have a higher complication rate.

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Intestinal rehabilitation in Latin-America, report of the first paediatric case treated with Teduglutide, fifty weeks of follow up

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Objectives and Study: Intestinal adaptation is a natural process that starts immediately after the establishment of the intestinal failure. There are several medical and surgical strategies employed to enhance this process. Recently, the use of Teduglutide has been approved for this purpose. Glucagon-like peptide 2 is an intestinal hormone that has specific trophic effects on the small and large intestine; Teduglutide, is its recombinant analogue. We aim to present the first case in Latin-America of a paediatric patient with short bowel syndrome and chronic intestinal failure that achieved enteral autonomy with the use of Teduglutide.

Method: Case Report, prospectively filled clinical data

Results: This is a 6 year-old boy full term delivered with intestinal atresia. He underwent surgery on the second day of life; the remnant intestine was composed of 20 cm of jejunum anastomosed to 3 cm of ileum with ileocecal valve and colon. After 3 other surgeries due to intestinal obstruction, he was sent home on PN and enteral nutrition, no oral foods due to oral aversion. At 11 months of age a STEP procedure was performed, the final bowel length was 86 cm of small bowel with ileocecal valve and the entire colon. He was readmitted several times due to line sepsis and catheter replacements complicated with central veins thromboses. When he was 3 years of age, he was referred to this Center. A reSTEP procedure was performed reaching a small bowel length of 133 cm after the surgery. With intense medical management, including anti motility medications, cyclic bowel decontamination, enteral feedings and enteral hydration, PN was progressively tapered to 3 days/week but the patient didn't tolerated it due to diarrhoea, weight loss and electrolyte disturbances. He was placed on PN 6 days/week. He developed central vein thrombosis, with further loss of accesses and was placed on the intestinal transplant waiting list with a femoral catheter as the last conventional central access available. His BMI/A was -0.69, and H/A - 2.42. At that point Teduglutide was approved in Europe for paediatric patients and it was offered to this patient in Argentina as an orphan drug. When this treatment started the patient was 6 years old and his BMI/A 1.32; H/A -3.66. The protocol consisted of a daily dose of 0.05 mg/kg administered subcutaneously. No adverse effects occurred. Enteral tolerance progressively improved and diarrhoea decreased. Nocturnal enteral feedings were increased and PN progressively decreased paired with weight and height progression (see table 1). PN was discontinued 25 weeks after starting treatment with Teduglutide. The BMI/A was 0.62, H/A -2.54, citrulline level was in the normal range (19 umol/l). The central catheter was electively removed 8 weeks after PN discontinuation. The patient has maintained his nutritional status (BMI/A 0.54; H/A -2.51) and laboratory values have maintained within the normal rage. He currently continues on daily treatment with Teduglutide, week 50.
Conclusion: From our perspective Teduglutide can be offered to selected patients with chronic intestinal failure that failed intestinal adaptation with medical and surgical strategies. Larger groups of patients are needed to better define the timing of the Teduglutide indication in children and its long-term effects.

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Evaluation of upper gastrointestinal system endoscopy signs in children diagnosed with fmf

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Objective: The objective of this study is to compare the upper gastrointestinal system complaints, endoscopical and histopathological findings of patients who had been diagnosed with Familial Mediterranean Fever (FMF) with the control group.

Materials and methods: Eighty five (85) cases aged between 4 and 18 who had been followed with FMF diagnosis between the years of 2012-2016 according to Livneh FMF Identification Criteria were included in the study as the patient group. Those cases in the patients' group had abdominal pain complaints despite the colchicine treatment, dyspepsia, retrosternal burning, acid regurgitation, no weight gain and growth retardation. Likewise, eighty five (85) cases followed by Gastroenterology Clinic with chronic abdominal pain were included in the study as control group. Demographic data and results of upper gastrointestinal tract endoscopy and biopsy findings together with the FMF gene analysis' results were recorded retrospectively from the cases' files. Data were analyzed using SPSS 15.0 program. Ratios in the groups were compared with chi-square test. A p value of < 0.05 was considered statistically significant.

Results: There were 27 males and 58 females with the mean age of 11,1±3,5 years in FMF diagnosed patient group. Eighty five (85) cases of the control group enrolls 49 females and the mean age was 11,5±3,8. Ongoing abdominal pain despite the treatment was observed in 69 % of the FMF diagnosed cases. Besides, 22 % of the cases showed dyspeptic complaints, and another 22 % had retrosternal burning. 33 % of the FMF group showed more than one complaint. Endoscopical examination revealed esophagitis in 54 %, esophagogastrid in 45 %, duodenitis in 25 % and duodenal ulcer in 1 % of the patients group. None of the abnormal findings were observed in 6 % of the patient group. Statistically significant decline in abnormal endoscopic findings were recorded in FMF group when compared with the control group (p < 0.001). Esophagitis in 89 %, esophagogastrid in 93 %, duodenitis in 73 %, esophagogastroduodenit (pangastrit) in 68 % and duodenal ulcer in 1 % of the cases in the control group were observed. During inspection of histopathological findings of FMF diagnosed cases, 67% of esophagitis, 65 % of inactive chronical gastritis, 44 % of active chronical gastritis and 13 % of duodenitis were observed. Besides, 53 % of esophagitis, 51 % of inactive chronical gastritis, 47 % of active chronical gastritis and 13 % of duodenitis were detected in control group. There were not any statistically significant variation observed between the histopathological findings of two groups. Only significant difference between the groups was the positivity of H. pylori in gastric antrum which is statistically higher in patient group (p: 0.003). FMF gene analysis of 35 patients showed the highest frequency for R202Q heterozygote mutation. There were not any significant correlation observed between the mutational analysis and endoscopical and histopathological findings.

Conclusion: Although we can not conclude with a clarified comment, we have been thinking that those cases with R202Q heterozygote mutation need to be investigated in terms of gastrointestinal system findings and failed colchicine treatment with larger scale studies.

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Management guidelines for infantile onset lysosomal acid lipase deficiency

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Objectives and Study: Infantile onset lysosomal acid lipase deficiency (LALD, Wolman disease) is an ultra-orphan, rapidly progressive lipid storage disorder with death before the first birthday in untreated infants. The main affected organs are the intestines and the liver, with lipid storage leading to malabsorption and liver failure, respectively. Survival in this cohort has been transformed with the licensing of Sebelipase alfa, a recombinant enzyme replacement therapy (ERT), and in clinical trials approximately 2/3 of infants are surviving beyond 1 year, with the oldest treated subject now over 6 years old. Despite this dramatic response not all infants are surviving and multidisciplinary management especially in the first year after diagnosis can be challenging, often requiring many months in hospital. Progression of disease in the first few weeks of life before diagnosis can be very rapid and urgency is required in suspicion, diagnostic confirmation and initiation of disease-modifying therapy. Early problems often involve an inflammatory process, hepatic dysfunction, severe gastrointestinal disturbance and growth failure. In the longer term, nutritional and gastrointestinal problems predominate. Development appears normal in the longer term. Infusion-associated reactions are not infrequent but can be managed. Guidelines to improve outcomes and improve the care of children with this disease are urgently required.

Methods: Through an iterative process involving those specialists and centers caring for the over 30 infants treated with Sebelipase alfa thus far, guidelines to aid in all aspects of the management have been sought through open discussion and voting among the group. Given the small number of treated infants thus far any guidelines will be based on a small amount of evidence and thus provisional.

Results: Guidelines for the management of LALD at the new era of available ERT have been outlined by a group of experienced specialists including recommendations regarding diagnosis, stabilization and initiation of ERT, nutritional support, dealing with immunological complications and defining a new dosing range. The role of biomarkers and the interplay of dietary lipid content and ERT dosing were also addressed.

Conclusion: In the new era of available treatment for children with LALD, experience-based guidelines for enzyme replacement therapy and nutritional care are available to guide the management of this complex disease.


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Mining rules for medical text annotation

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Objectives and Study: Electronic Medical Records contain free form text descriptions of a patient’s condition or investigations (e.g., endoscopies), some in an informal manner. Extracting and structuring information out of them is crucial for further automatic processing or various statistical analysis. Our project was focused on solving these challenges with minimum human intervention. The solution we propose has two stages:

1. based on a set of medical texts annotated by a human, automatically generate rules which associate a formal annotation with some word sequences present in the corresponding description
2. rules produced in stage 1 are validated by a human expert, then applied to annotating new texts automatically.

The main goal was to come up with a solution able to free the human agent from the burden of reading the whole text and extracting the information of interest.

Method: A set of 735 endoscopy descriptions, in Romanian, manually annotated by a human expert was used. It contained 829 distinct words (accounting for 7406 occurrences).
A modified version of the Apriori algorithm was used for generating association rules between texts and annotations. It produces rules of type X → Y, meaning that “whenever X, it follows Y”. This version allowed filtering rules by form (e.g., having solely an annotation on the right hand side of the arrow (Y)), support (which for all experiments was set to 0.3) and confidence (which was set to 0.85). Rules are further filtered in order to eliminate trivial ones like those comprising prepositions only etc.
Then, the rules are ordered according to the set of examples covered and presented to the user, who could either approve the topmost one or choose another one(s). After some rules are picked and saved, examples covered by them are eliminated and the process continues.

Results: We performed several experiments, each aimed to build associations between word sequences and annotations, with 3 sets of association rules built each time. Rules were ranked based on a heuristic designed to maximize the likelihood to be confirmed by a human. In each experiment, after three such iterations, we ended up with a bunch of rules covering at least 93% of the annotated examples. They could be employed for automatically annotating new texts.
The table shows the percentage of examples covered by rules generated in every iteration. The values with no asterisk result by applying the rules suggested by the algorithm. The ones with an asterisk correspond to manually selected rules. In about three quarters of cases, the rules suggested by the algorithm were confirmed by the human specialist.

<table>
<thead>
<tr>
<th>Rule head</th>
<th>Iteration 1</th>
<th>Iteration 2</th>
<th>Iteration 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>StomachLumen=Incomplete Gastric Volvulus</td>
<td>80%</td>
<td>91,25%</td>
<td>98,75%</td>
</tr>
<tr>
<td>StomachLumen=Duodenogastric Reflux</td>
<td>62,5%</td>
<td>81,25%</td>
<td>93,75%</td>
</tr>
<tr>
<td>StomachAntralMucosa=Nodular</td>
<td>43,93% *</td>
<td>44,35%</td>
<td>99,16%</td>
</tr>
<tr>
<td>StomachBodyMucosa=Erythematous</td>
<td>100% *</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Pilor=Spastic</td>
<td>80% *</td>
<td>90%</td>
<td>95%</td>
</tr>
</tbody>
</table>

[Percentages of examples covered by the rules]

Conclusion: A solution for extracting structured information from raw medical texts has been proposed. Starting from a set of annotated texts, associations between text fragments and their corresponding annotations are built. The solution is semi-supervised in that the rules could be selected manually by the user, who can override the suggested choice. No language specific tools have been
Experiments on a set of text descriptions of endoscopies in Romanian showed the automatically annotated texts agree in a high proportion to the manually annotated ones. Typically, up to three rules cover most of the examples, with only several cases remaining to be dealt with manually.

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Fecal microbiota transplantation is effective in children with autistic spectrum disorders

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Objectives and Study: The prevalence of children with autistic spectrum disorders (ASD) is increasing worldwide (1). The cause of ASD is poorly understood and involves interplay of different genetic and environmental factors where gut microbiota could have a significant impact. The aims of the study were to evaluate fecal microbiota transplantation (FMT) effectiveness in children with ASD in treating autistic spectrum disorders and gastrointestinal (GI) symptoms.

Method: We performed FMT in 4 boys (5-8 yrs., every months, three times for every patient) with ASD and mild GI symptoms. The donor was the same 7 yrs. old healthy, unrelated girl. Her feces were infused into the cecum during colonoscopy. The patients' gut before FMT was prepared with polyethylene glycol 4000 (Fortrans). Symptoms were checked every week after FMT with parent global impression score (PGI-R; the symptoms were rated on a scale of 1-7, where 1= much worse, 7= much better compared to baseline) (2) for ASD and gastrointestinal symptom rating scale (GSRS; 1 represents absence of troublesome symptoms and 7 represents very troublesome symptoms) (3).

Results: We filled GSRS and PGI-R scores by asking parents about their child's health during phone call or when the patient came to the hospital for FMT. The total GSRS and PGI-R scores improved in all patients after FMT (Table 1). The best improvement was seen after 2 wk. post FMT, less before second and third FMT. The FMT treatments were generally well-tolerated, without adverse effects.

<table>
<thead>
<tr>
<th></th>
<th>Before FMT</th>
<th>After 2 wk. post FMT</th>
<th>After 1 mo. post FMT</th>
<th>After 2 mo. post FMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSRS</td>
<td>34.25</td>
<td>20</td>
<td>22</td>
<td>22.25</td>
</tr>
<tr>
<td>PGI-R</td>
<td>-</td>
<td>54</td>
<td>51.5</td>
<td>50.75</td>
</tr>
</tbody>
</table>

[Table 1. GSRS and PGI-R scores before and after FMT]

Conclusion:
1. FMT has positive effect on GI and autistic spectrum disorders symptoms.
2. The FMT treatments were well-tolerated.

References:

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GASTROENTEROLOGY - Gastroenterology other

G-P-199

Congenital chloride diarrhea prenatally misdiagnosed as intestinal atresia

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Objectives and Study: Congenital chloride diarrhea (CCD) or chloride losing diarrhea is a rare autosomal recessive disease with chronic secretory diarrhea. Mutations in the solute carrier family 26 member 3 (SLC26A3) gene encoding for a transmembrane Cl⁻/HCO₃⁻ exchanger cause CCD. Here we report a case with CCD presenting with a history of prenatal suspicion of intestinal atresia.

Method: A baby girl of first degree cousin Turkish parents was born at 35 week gestation via cesarean section with 2300 gr weight. The antenatal course was complicated by maternal polyhydramnios and honeycomb looking fetal bowel loops with a diagnosis of probable jejunal atresia. She was followed at neonatal intensive care unit because of abdominal distension and lack of meconium passage, with suspicion of intestinal atresia. However radiographic contrast enema revealed no intestinal obstruction. After the meconium passage on the third day enteral nutrition was started. Afterwards she produced voluminuous stools, hyponatremia and hypochloremia together with metabolic alkalosis. Results of fecal electrolytes were Na: 97, Cl: 137 mEq /dl. As these were confirmed with repeated analyses, CCD was diagnosed. Oral sodium chloride supplementation was started at a dosage of 5 mEq/kg., and metabolic balance was gained together with weight gain. Genetic testing revealed a homozygous c.G1954A (p.D652N) mutation in exon of the SLC26A3 gene confirming the diagnosis of CCD. She is now 5 months-old weighing 8360 g (1.32 SD) and has been breastfed till now passing 2-3 stools each day and showed no episodes of dehydration. She still receives 2 mEq/kg NaCL.

Results: Antenatal clues as maternal polyhydramnios, dilated fetal loops and preterm birth can be important for diagnosis of CCD, sometimes hard to differentiate from congenital intestinal abnormalities. After birth profuse watery diarrhea usually causes electrolyte imbalance (hypochloremic metabolic alkalosis or hyponatremia)and dehydration. High fecal chloride level can be a clue for the diagnosis and it should be confirmed by genetic analysis.

Conclusion: As the disease is rare, early diagnosis and treatment can prevent short and long term complications and lead to better outcomes for infants as in our case.

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**Diagnosis and management of cow’s milk protein allergy - how big is the gap between ideal and reality? A quality-of-care survey in Europe**

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**Objectives and Study:** In 2012 the ESPGHAN published guidance for diagnosis and management of cow’s milk protein allergy (CMPA)[1]. We conducted a quality-of-care survey across Europe to evaluate the implementation in primary care practice.

**Methods:** From 2/2015 to 12/2016, an anonymous online-survey was sent to pediatricians and/or general practitioners in 13 countries (Croatia, Czech Republic, Finland, Germany, Greece, Hungary, Italy, Poland, Romania, Slovenia, Spain, Sweden and The Netherlands). Participants were invited via email by their respective medical association. The survey included demographic questions and medical case-examples with multiple-choice answers regarding CMPA management.

**Results:** In total 2551 physicians completed the survey (72% female, 86.8% pediatricians). Being asked how to exclude CMPA in a 10-month old infant with chronic diarrhea and failure to thrive, 68% correctly chose an elimination diet and challenge procedure in case symptoms improve. However, 19% regarded a negative specific IgE result and 8% a negative skin prick-test as sufficient to exclude CMPA, while 5% would eliminate lactose. The question which other formulas are allowed for an infant diagnosed with CMPA, but refusing extensively hydrolyzed formula, was correctly answered by 63% with amino acid-based and 51% soy-based formula, but 19% considered partially hydrolyzed, 11% goat’s milk-based and 6% lactose-free cow’s milk-based formula as adequate. The question what to advise in a so far exclusively breast-fed 5 month-old infant developing swelling of lips and eyelids on drinking his 2nd bottle of infant formula, was correctly answered by 26% to resume complete breastfeeding under usual diet of the mother, while 46% would advise breast-feeding under maternal elimination of dairy products, 21% would switch to an extensively hydrolyzed and 6% to an amino-acid-based formula. Being asked what to advise for the same child in terms of complementary foods (CF), 53% would start but strictly avoid CMP, while 15% would also eliminate other potent allergens until 12 months, 25% would recommend CF after 6 months and 5% would start without any restrictions. When having tested this child negative for specific IgE, 46% would still perform supervised CMP challenge, 36% would continue elimination diet until 12 months, 7% would consider CMPA as unlikely, 6% would test C1-esterase-inhibitor-deficiency and 5% for IgG against CMP.

**Conclusions:** Our results disclose major deficits in the management of CMPA, particularly how to test, when to perform elimination diet and what types of infant formulas to use. Appropriate dissemination and training activities in primary health care settings are needed.
Reference:

Disclosure of interest: This study was financially supported by Nestlé Health Science, Switzerland. The company had no influence on content, analysis or interpretation of the survey.
Awareness, attitude and usage of probiotics for the prevention of antibiotic-associated diarrhoea among caregivers and doctors in Poland: cross-sectional study.

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Objectives and Study: Probiotics are widely used for various clinical indications, however, only a few of them were proven to confer a health effect on the host. Probiotics are strain and dose dependent. Lactobacillus rhamnosus GG and Saccharomyces boulardi are recommended by ESPGHAN for the prevention of antibiotic-associated diarrhoea (AAD). The cross-sectional study aimed at obtaining data on awareness, attitude and usage of probiotics for AAD prevention among caregivers and doctors in Poland, and analysing the sources of recommendation and selection of probiotic preparations.

Method: The study included a self-administered survey of the caregivers of children hospitalised in Public Paediatric Teaching Clinical Hospital in Warsaw, or consulted in the outpatient clinic. The survey evaluated caregivers' opinion of probiotics efficacy in AAD prevention, whether they used them for AAD prevention, which probiotic product (under the trade name) was used and who advised its administration. Inclusion criterium was the use of antibiotics in the community setting by their children within the last 12 months.

Probiotics were classified based on strain specificity and CFU dosage in three categories: 1) medicinal product with proven efficacy, 2) non-medical product with proven efficacy (e.g. food supplement or food for particular nutritional use) and 3) other preparations without proven efficacy. Furthermore, the survey showed who advised a specific preparation: a doctor, pharmacy employee or a person unrelated to medicine. Lactobacillus rhamnosus LGG and Saccharomyces boulardii in the dose ≥5 billion CFU/day were considered as of proven efficacy.

Results: A total of 463 questionnaires revealed that probiotics were used during antibiotic therapy in 99.4% (456/463) of cases. 34 patients used products that were classified as medicines with proven efficacy, 156 used non-medical products with proven efficacy, 162 patients used preparations without proven efficacy. 104 caregivers could not recall the trade name, 7 did not use probiotic products.

The majority of caregivers (82%, n: 378/463) believed that probiotics are effective in AAD prevention, 6% (n: 28/463) were of the opposite opinion, 12% (n: 56/463) did not express opinion on that matter. In 87% (n: 397/456) of cases probiotics were advised by doctors, out of which 56% were products with proven efficacy. 5.5% probiotic products were based on pharmacy employee recommendation, however only 32% of them had proven efficacy. Surprisingly, persons unrelated to medicine (7.5%) recommended products with proven efficacy in 48% of cases. In 7 cases caregivers did not indicate an advisor.

Conclusion: Our study showed a positive attitude of caregivers towards the use of probiotics for AAD prevention who followed the recommendations of advisors. However, almost half preparations (in majority advised by doctors) were without proven efficacy. In case of AAD occurrence, due to the lack of effective prevention, the negative consequence might lead to the loss of trust in probiotics effectiveness and unjustifiably increase the cost of AAD prevention with no certainty of effectiveness.
Effect of age, anatomic location and stage of PGIL on the prognosis: A multicenter retrospective analysis of 87 cases aged ≤ 18 years from central China.

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Objectives and Study: To investigate the anatomic distribution and clinical stage on the prognosis of ≤18 years old patients with PGIL.

Method: We retrospectively analyzed 87 PGIL cases of ≤18 years old from multicenters in central China. PGIL was diagnosed according to Dawson's criteria. The pathological samples were confirmed based on WHO-2015 criteria for lymphoid malignancies.

Results: The lesions were located in the small intestine in 51 (58.6%) cases, ileocecal region and appendix in 29 (33.3%) cases. Pathological examination showed 41 (47.2%) cases of DLBCL and 37 (42.5%) cases of BL. Prognosis analysis showed 46 (50.6%) cases survived, 36 (41.4%) cases died and 7 (8%) patients were lost for follow-up. Univariate analysis showed that age, lesion site, clinical stage and chemotherapy were related to the prognosis (P &LT; 0.05). The prognosis and 3-year survival of stage I+II patients were significantly higher than those of stage III+IV patients (P &LT; 0.001). Multivariate COX regression analysis showed that the mortality of patients who did not receive or only received partial chemotherapy was 3.4 times higher than those underwent the full course chemotherapy. The risk of death in patients with ascites was 1.8 times higher than those without ascites.

Conclusion: When patients have unexplained weight loss or gain, anemia, abdominal pain, or abdominal mass, they should be considered PGIL. Most of PGIL are pathologically classified into DLBCL and BL. It is also important to understand the location of onset and clinical stage on prognosis

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Prevalence of cow’s-Milk protein allergy in a primary paediatric practice in Croatia

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Objectives and Study: Aim was to evaluate the prevalence of Cow’s-Milk protein allergy (CMP) among infants in our practice. Cow’s-milk protein allergy is the leading cause of food allergy in infants, therefore the challenge remains to make correct diagnosis while minimizing the burden to patient and family.

Method: We retrospectively collected and analyzed electronic data of children aged 1-12 months in our primary paediatric practice. Descriptive statistical analysis was used.

Results: From a total of 250 patients aged 1-12 months, 25 children (10%) had cow’s-milk allergy, of which 10 (40%) had atopic eczema, 5 (20%) had blood and mucus in stools, 3 (12%) patients had failure to thrive, 3 (12%) had urticarial rash after administering cow’s-milk formula, 2 (8%) had iron-deficiency anaemia, and 2 (8%) patients had recurrent wheezing, atopic eczema and failure to thrive combined. Mean age at diagnosis was 3 months. All patients had positive skin prick test and significantly elevated levels of whole cow’s milk specific IgE. Patients mostly had specific IgE levels class 3, with elevated total IgE levels. The 2 patients (8%) with cow’s milk allergy, wheezing and atopic eczema combined had specific IgE levels class 4 and also sensitization to soy protein. Extensively hydrolyzed formula was prescribed in 10 (40%) cases, in 2 (8%) cases amino acid based formula with severe atopic eczema in consultation with gastroenterologist and dermatologist, in most cases 13 (52%) mothers were advised to breast-feed without all milk and milk products from their own diet. Most cases of CMP allergy resolved by the age of 18 months, only 2 children with severe atopic eczema had amino acid based formula by 3 years of age.

Conclusion: Cow’s-milk protein allergy is a common problem in primary paediatric care, often accompanied with atopic eczema, wheezing and failure to thrive, diagnostic criteria should be applied to minimize misdiagnosis and referral to paediatric gastroenterologist only when needed.

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Rectal hypersensitivity in children with chronic constipation and faecal incontinence

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Objective and Study: Awake high resolution anorectal manometry (AHRAM) is the investigation of choice for adults with faecal incontinence (FI), evacuation difficulties and chronic constipation (CC). Definition of Rectal hypersensitivity (RH+) has been extrapolated from our adult gastrointestinal physiology unit, due to limited paediatric data. RH+ has been defined as reduced sensory threshold - to balloon distension, which is associated with increased bowel frequency, reduced ability to defer defecation, increased pad usage, and negative lifestyle effects ¹. In adults, RH+ has been useful in understanding the pathophysiology of their bowel condition, rather than taxonomy based on symptoms alone, which has improved their management. RH+ has not been described in children. There is a paucity of consistent studies of AHRAM in children. We describe RH+ in children with CC/FI using AHRAM.

Methods: Prospective data was collected from the Children's Anorectal Physiology Service (CAPS) (September 2016 to December 2017 - 15 months) with CC/FI, who have failed conservative treatments (>2 years). All had AHRAM, bowel assessments (St Mark's Incontinence Score [SMIC], Cleveland Constipation Score [CCS]), transit studies and psychosocial assessments. Management was discussed in our weekly specialised MDT with our multi-professional team. Demographic data was collected.

Results: Total number of patients evaluated was 94 AHRAM: 53/94 (56%) were male, median age was 9 (range 17 months - 16 years), diagnosis was idiopathic CC (67%), ARM (13%), Hirschsprung disease (11%), trauma (2%) and joint hypermobility (7%). RH+ was demonstrated in 20% (19/94): 52% female; median age 9 (range 3-16). SMIC was abnormal in 84% (16/19) and CCS in 89% (17/19). Only 57% (11/19) patients presented with faecal urgency in their medical history and questionnaires. Patients scored the severity of their symptoms: median score 9 (10 severe; range 7-10). At least half (9/19: 47%) also presented with urinary incontinence. Regarding sphincter function: all had normal squeeze pressures and 5/19 (26%) had low resting pressures. Five patients (26%) were at risk of psychological distress. Based on MDT discussion, there were multiple management approaches for this group including psychological support (32%), transanal irrigation (26%), medicine modification/modifying toileting regime (36%), intersphincteric botox (26%) and biofeedback (11%).

Conclusion: Rectal sensation is easily measured in children. This novel physiological parameter has refined our management of children with CC and FI.
1. Symptom evaluation does not necessarily predict RH+
2. RH+ cannot be interpreted in isolation
3. We suggest comprehensive evaluation of symptoms, transit, SMIC, CSI, psychosocial evaluation, AHRAM (sphincter function and rectal sensation) to allow optimal assessment and tailored therapy
4. Squeeze pressure were normal in all our patients
5. Intersphincteric botox and psychological support has a role (interruption of sensation) has modified clinical outcomes
6. RH+ may be a symptom of anxiety - that is best managed by psychological intervention


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**GASTROENTEROLOGY - GI motility, GERD and functional GI disorders**

G-P-205

**The relationship between functional constipation and sleep disorder in children; a case-control study**

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**Objectives and Study:** Childhood constipation is a common gastrointestinal disorder. Some studies indicate that in 90-95% of children, there are not any distinct organic reasons for constipation and only 5-10% of patients have distinct organic reason. Studies have shown that psychological distresses, environmental factors and insufficient sleep are related with functional diseases of digestive system. Therefore, the aim of the present study is to evaluate the correlation between sleep disorders and functional constipation in children.

**Method:** The present study was a case control study in which 176 children in age range of 2-6 years referring our Hospitals were evaluated for indices of sleep disorder in two groups from March 2016 to March 2017, one group children with functional constipation (88 individuals) and healthy children (88 individuals). The functional constipation was diagnosed after history taking based on ROM III criteria. On the other hand, the sleep disorder was calculated using children’s sleep Habits Questionnaire (CSHQ) and the scores of each part were calculated separately. Furthermore, the demographic data, urine specific gravity and Socio environmental factors as the duration of TV watching, breakfast using, having breakfast and dinner with parents, education level of parents, Using public toilet ... were recorded for both groups.

**Results:** The results showed that there was no significant difference between the two evaluated groups for age, gender, weight, education level of parents, water drinking during night, (P>0.05), however, there was significantly difference between two groups in having breakfast, having breakfast and dinner with parents, the duration of TV watching, Using public toilet, and urine density (P&LT; 0.05). In evaluation of sleep disorder, although no differences were observed among the both groups totally (P>0.05), their subgroups such as delay in onset of sleeping and parasomnia and sleep respiratory disorder showed a significant difference in constipation involved group comparing to the healthy group (P&LT; 0.05), however, no significant differences were seen in other cases such as bedtime and daytime sleepiness (P>0.05).

**Conclusion:** With regards to the above findings, there was a significant correlation between constipation and sleep disorder and Socio environmental factors and since improving of agents leading to continuity of normal bowl habit in primary stages, can prevent their development into chronic status, Attention to sleep disorder and its treatment can prevent the occurrence of functional constipation in children.

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Timing of passage of meconium and bowel habits at six months in late-preterm infants: Preliminary data

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Objectives and Study: An association between preterm birth and delayed passage of meconium (PoM) has been demonstrated. The possibility that timing of PoM may influence bowel habits at age 6 months has never been investigated in late preterm infants.

Method: Healthy neonates born at a gestational age (GA) > 34 weeks but < 37 weeks were consecutively enrolled. Gender, birth weight (BW), mode of delivery and timing of PoM were recorded. Six months after birth, parents were asked to complete a questionnaire on their child's bowel habits (Rome IV Diagnostic Questionnaire).

Results: We enrolled 172 newborns (94 males). Median GA was 36 weeks (range, 34-36+6 days). Median BW was 2450 g (range, 1450-3800), with 30 (17.5%) small for GA (SGA) newborns. Most infants (60.3%) were born by cesarean section. Meconium was passed within 24 hours in 122 newborns (71.4%) and within 48 hours in the remaining cases. No correlation was found between timing of PoM and BW, GA, mode of delivery or proportion of SGA newborns (p>0.3). Similarly, no correlation was detected between timing of PoM and bowel habits at age 6 months. Particularly, infants who passed meconium before 24 hours and those with PoM between 24 and 48 hours did not differ in terms of evacuation of huge stools, fecal retention, stool frequency and consistency (p>0.1).

Conclusion: These preliminary data suggest that timing of PoM does not affect bowel habits at age 6 months in late preterms. Other environmental factors are likely to determine bowel patterns in the first months of life.

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Prevalence of dumping syndrome after a surgery for oesophageal atresia Type C without fundoplication

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Objectives and Study: Dumping syndrome (DS) is most frequently described as a complication of anti-reflux surgery in children. We recently reported two cases of DS in children operated with oesophageal atresia (OA) at birth, without any other surgery. We therefore formulate the hypothesis that DS could occur in OA independently from a fundoplication. The primary objective of the study was to evaluate the prevalence of DS at 3 months of age in infants operated at birth with type C OA. The secondary objectives were to describe symptoms and clinical features of infants presenting with DS and to look for risk factors of DS in OA.

Methods: We conducted a prospective multicentric study including infants with type C OA. Before the age of 3.5 months and as soon as they weighted more than 4.150 kg, patients underwent an oral glucose tolerance test (OGTT). Glycemia was measured every 30 minutes for the first 2 hours and every hour until 4 hours after 1.75 g/kg oral glucose intake. DS was defined as early hyperglycemia (more than 1.8 g/L until 30 minutes, > 1.7 g/L between 30 minutes and 2 hours and > 1.4 g/L between 2 and 3 hours) and/or late hypoglycemia (less than 0.6 g/L after 2 hours).

Results: Thirty eight patients completed OGTT, 11 of them (29%) had a DS diagnosed. None of the following clinical characteristics: weight at birth, prematurity, associated malformation, enteral nutrition nor conditions of the surgery including tension of the anastomosis, need for colic or gastric plasty or visualization of vagus nerve) were statistically associated to the occurrence of a DS. Post prandial diarrhea, abdominal pain and bloating were significantly associated with early DS (p= 0.035) and pallor, hypotonia, agitation, seizure, drowsiness, sweating were associated with late DS (p=0.035). However none of these signs were specific of DS as they were as frequent in OA patients without DS.

Conclusion: The high frequency of DS without identified
Etiology and outcome of children with chronic intestinal pseudoobstruction

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Objectives and Study: Chronic intestinal pseudo-obstruction (CIPO) is a severe form of gastrointestinal dysmotility with recurrent episodes of intestinal subocclusion mimicking a mechanical obstruction. This study aimed to evaluate the patients with CIPO followed up at our center.

Method: Thirteen patients with CIPO who were admitted between February 2012 and November 2017 were evaluated retrospectively. Demographic data, clinical features, medical and surgical treatments, nutritional support, treatment response, small intestinal transplantation and survival were evaluated.

Results: The mean age of application to our clinic was 30.2 ± 40.7 months (minimum 1.5 - maximum 132 months). One patient had premature birth history. Two patients were diagnosed at 1 and 9 years, respectively, and all other patients were diagnosed at neonatal period. Three patients were diagnosed as antenatal megacystis-microcolon-intestinal hypoperistalsism. All the patients had vomiting complaints. Abdominal distention in 92.3%, chronic constipation in 23%, the most common cause of admission. Intestinal neuronal dysplasia in 3 patients, enteric anendocrinosis in 1 patient and clinical findings in 2 patients with Wardenburg syndrome were diagnosed in patients with bowel biopsy. Megasistis was present as an additional malformation in five patients. In only 5 patients, medical treatment response was possible during pseudoobstruction episodes. In the follow-up, venous thrombosis developed in 3 patients and impairment in liver function tests developed in 2 patients. Postpiloric feeding was tried in 4 patients but was not beneficial. Nutrition with gastrostomy was tried in 7 patients, but only three patients could be fed. Four patients tolerated oral feeding over time. 3 patients underwent small bowel transplant. Graft dysfunction developed in a 2-year-old patient and was waiting for retransplantation for one year. The patient who had a 9-month-old small intestine transplant was died after one year later. One patient is followed up for 4 years after transplantation. 2 patients were dependent on TPN, and 1 patient received partial PN support. 3 patients are being followed by gastrostomy, 1 patient is being followed ileostomy and 1 patient is being followed by jejunostomy. 2 patients were exitus and 3 patients did not continue their follow-up. 3 patients are being followed up with intermittent conservative treatment without ostomy caused by recovered pseudoobstruction attacks.

Conclusion: CIPO is a rare disease that can show different clinical signs. While some patients require small intestinal transplantation, supportive care may be sufficient in some patients during exacerbations. For this reason, each patient should be evaluated in terms of treatment strategy within themselves.

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Relationship between meal-related symptoms and gastric emptying in children with functional dyspepsia

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Background and aims: Functional dyspepsia (FD) is a common disorder in children and adolescents. Suggested underlying pathophysiological mechanisms are mainly delayed gastric emptying, impaired gastric accommodation and visceral hypersensitivity to distention. The primary objective of the study was to assess the relation between self-reported symptoms of functional dyspepsia after ingestion of a meal and results of gastric emptying breath test.

Methods: Thirteen patients (23.1% males, 76.9% females, 10.7±2.75 years old) underwent a ¹³C-octaenoic breath test and filled out a questionnaire about functional dyspepsia symptoms at each breath sampling after ingestion of a standardised test meal (15 minutes interval for 240 minutes).

Results: Most frequent reported meal-induced symptoms were epigastric pain (92.3%), postprandial fullness (76.9%), early satiety (76.9%) and nausea (76%). A delayed gastric emptying time (>p75) was shown in 61.5% of patients. Severity scores for overall FD symptoms and bloating, postprandial fullness and early satiety are higher in patients with delayed gastric emptying. Severity scores for nausea and epigastric pain are higher in patients with normal gastric emptying. None of these results reached statistical significance. Symptom severity scores for bloating, nausea, satiety, fullness and epigastric pain increased after ingestion of the meal. Symptom severity scores for belching and pyrosis were not increased after ingestion of the meal.

Conclusion: In children and adolescents with functional dyspepsia, a subgroup with delayed gastric emptying shows a trend towards higher symptom severity scores for bloating, postprandial fullness and early satiety. In the subgroup with normal gastric emptying higher scores for epigastric pain and nausea are seen.
Laxative choice and treatment outcomes in childhood constipation: clinical data in a longitudinal retrospective study

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Objectives and study: Functional constipation (FC) is a common gastrointestinal (GI) problem affecting children’s well-being and quality of life. Although polyethylene glycol (PEG) is recommended as the first line therapy, it is not always applicable in lower socioeconomic populations. Hence, this study aimed to compare clinical courses of FC in children treated with different medications in order to identify prognostic factors related to treatment outcomes.

Methods: We reviewed the medical records of patients aged ≤15 years diagnosed with FC according to the ROME IV criteria from 2007 to 2015 at the GI clinic, Songklanagarind Hospital. Baseline characteristic, medical history, and treatment outcomes were collected at first and subsequent visits.

Results: 104 patients (median age at diagnosis: 2.8 years) were diagnosed with FC. The number of follow-up visits per patient ranged from 1 to 35. The median duration of follow-up was 18.0 months (range 6.0-84.2 months). PEG without electrolyte (PEG4000; Forlax®, Ipsen, France) was given to 21% of patients; only 7 patients were prescribed PEG at the first visit, while the others were switched from another medication during their follow up visits. The median age at diagnosis and age of onset were not different between patients who received PEG (PEG group) and those who did not (non-PEG group). However, the duration of symptom to diagnosis in the PEG group was significantly longer than that of the non-PEG group (P = 0.048). During the follow up period, 76% of patients experienced first recovery with a median time to recovery of 9.8 months. At 1 year follow up, 54% of the patients had successful outcomes after stopping medication. This percentage increased to 78% if asymptomatic patients still receiving medication were included. There were no significant differences in time until first recovery and relapse between patients who received and those who did not receive PEG (P = 0.99 and 0.06, respectively).
### Treatment and outcome

<table>
<thead>
<tr>
<th>Treatment and outcome</th>
<th>All (n=104)</th>
<th>PEG group (n=22)</th>
<th>Non-PEG group (n=82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk of magnesia for maintenance phase at the first visit</td>
<td>93 (89.4)</td>
<td>14 (63.6)</td>
<td>79 (96.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PEG for maintenance phase at the first visit</td>
<td>7 (6.7)</td>
<td>7 (31.8)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of patients who had first recovery</td>
<td>79 (76.0)</td>
<td>16 (72.7)</td>
<td>63 (76.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Duration from first GI visit to first recovery, months (median, IQR)</td>
<td>7.8 (4.5, 16.0)</td>
<td>10.5 (5, 16.3)</td>
<td>7.4 (4.1, 15.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Number of patients who had ≥ 1 relapse</td>
<td>26 (25.0)</td>
<td>9 (40.9)</td>
<td>17 (20.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Outcome at last visit - Improve after first recovery</td>
<td>76 (73.1)</td>
<td>14 (63.6)</td>
<td>62 (75.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>- Persistent constipation</td>
<td>13 (12.5)</td>
<td>3 (13.6)</td>
<td>10 (12.2)</td>
<td></td>
</tr>
<tr>
<td>- Improve with medication</td>
<td>12 (11.5)</td>
<td>3 (13.6)</td>
<td>9 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Not improve after relapse</td>
<td>3 (2.9)</td>
<td>2 (9.1)</td>
<td>1 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

**[Treatment outcomes according to medication group.]**

Among those who recovered, 33% relapsed with a median time until relapse of 24 months (range 0.5-77.8). We found that patients who were > 6 years at diagnosis, presented with normal defecation frequency, had no history of CMPA, and had used PEG during the course of treatment were more likely to stop medication at an early time.

**Conclusion:** Treatment outcomes between patients who had and never had PEG demonstrated no significant difference in our real long-term follow-up study. Hence, current practices in laxative prescriptive patterns may be effective.
Objectives and Study: Fecal calprotectin (FC) is a marker of intestinal inflammation, helping in the diagnosis and monitoring of gastrointestinal disorders (GID) that have inflammation as a common denominator. At present, there is no established reference value in various gastrointestinal disorders in paediatrics except for the IDB. The objective of the study was to evaluate the HR ranges in organic and functional gastrointestinal disorders in paediatrics. Descriptive retrospective study 2013-2017.

Method: Patients ≤ 18 years of age attended in Gastronutriped were included, who were diagnosed with an organic or functional gastrointestinal disorder and HR was performed. The HR values were classified according to the National Institute for Health and Care Excellence (NICE) guideline: negative: less than 50 µg / g; mild: 50-100 µg / g; moderate 101-200 µg / g; severe: >200µg / g. It was processed by Immunoassay. The data were analyzed in Stata 13. For categorical variables, absolute and relative frequencies were used and for the continuous measures of central tendency and dispersion. The normality of the continuous variables was evaluated by the shapiro-wilk test. Difference was established between the groups by calculating p value with the wilcoxon test.

Results: 79 patients, with a median age of 24.5 months (interquartile range 59.5 months). 54.17% were male. 55.56% had malnutrition. 64.52% presented organic pathology and the main diagnosis was food allergy enteropathy (18.06%). The main diagnosis in functional disorders was constipation (25%). The median HR was 86.5 µg / g (interquartile range 197.65 µg / g). 33.33% had a normal HR range, 36.11% had a mild-moderate level and the rest was classified as severe. The main diagnosis in the normal range was post-enteritis syndrome (median: 14 µg / g), in the mild range - moderate was functional constipation (median: 118.65 µg / g), and in the severe range there were several organic disorders (intestinal lymphangiectasia and eosophilic esophagitis) and functional (colic and irritable bowel syndrome). Comparing the values of the FC and the type of GID, no statistical difference was found between organic vs functional (p = 0.1840).

Conclusion: There are some studies that suggest a different sensitivity and specificity of HR depending on each pathology and age. However, cutoff values for functional gastrointestinal disorders (FGID) have not been established in children. We found HR elevated not only in organic GIDs but also in FGID such as constipation, infantile colic and irritable bowel syndrome. FC would be useful as an inflammatory but non-specific inflammatory marker to determine organicity. We recommend performing multicentric studies with a larger sample of children with functional and organic gastrointestinal disorders in order to establish cut-off points for the different GIDs.

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Transcutaneous oesophageal ultrasonography in children with suspected gastro-oesophageal reflux disease

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Objective: To evaluate the oesophageal morphological parameters and liquid reflux using transcutaneous oesophageal ultrasonography (US) in children with suspected gastro-oesophageal reflux disease (GORD).

Materials and methods: Twenty-two children with suspected GORD and 23 healthy controls were enrolled from November 2015 to January 2017. GORD was defined as reflux index and/or liquid reflux evaluated by multichannel intraluminal impedance-pH (MII-pH) monitoring greater than 95th percentile of age-specific values. All subjects underwent transcutaneous oesophageal US for assessment of liquid reflux and oesophageal morphology.

Results: Median ages of patients (50% male) and controls (56.5% male) were 1.6 years (range 7.2 months - 5 years) and 1.7 years (range 6 months - 7.5 years), respectively. GORD symptoms were divided into oesophageal (n=11) and extra-oesophageal (n=11) manifestations. Occurrences of reflux and oesophageal morphological parameters detected by transcutaneous oesophageal US were not different between patients and controls. However, patients tended to have shorter abdominal oesophageal length (16.8±4.3 mm) compared with controls (18.2±6.5 mm). Patients with GORD confirmed by MII-pH monitoring (n=6) had higher cervical oesophageal wall thickness and diameter, abdominal oesophageal diameter, and degree of gastro-oesophageal angle than those with normal MII-pH monitoring. However, the differences were not statistically significant. The abnormal liquid reflux detected by trans-oesophageal US was not significantly different from abnormal reflux index and/or liquid reflux by MII-pH monitoring.

Conclusion: Visualizing refluxate, oesophageal morphology, and gastro-oesophageal angle evaluated by transcutaneous oesophageal US were not useful for diagnosing GORD.

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Prevalence of paediatric functional gastrointestinal disorders in the first year of life among healthy Malaysian infants

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Objectives and Study: Prevalence of paediatric functional gastrointestinal disorders (pFGID) varies but is unknown in Malaysia. The present study aimed to investigate point prevalence of pFGID in healthy Malaysian infants below one year.

Method: This was a cross sectional study, conducted in well-baby clinic in University of Malaya Medical Centre (UMMC), Malaysia. The clinic provides monitoring of infant well-being and vaccination. We adopted a universal sampling method and excluded any child with congenital disorders potentially affecting gastrointestinal functions, chronic debilitating diseases and hypothyroidism. During clinic visit, consented parents answered a Malay translated version of Questionnaire on Paediatric Gastrointestinal Symptoms - toddler (0-3 years), Rome IV version, sociodemographic data and clinical characteristics. Rome IV criteria were used to defined the cases of pFGID in this study. Hospital ethical approval was acquired. Descriptive, statistical analyses were performed.

Results: Of the total 534 infants recruited (rejection rate 6%), 54.1% were males; 92% were born term; mean [S.D.] age 6.8 [±3.4] months; mean birth weight of 2.97 [±0.47] kg. Ethnicity group consisted of 57.5% Malays; 26.2% Chinese and 15% Indians. Median household income was US$1711 (range 244-6357)/month. Mean mother and father's age were 31.9 and 33.9 years, respectively. 99.6% were married. Type of milk feeds were 36% exclusive breastfeeding; 29% formula feeding; and 35% mixed. Median age of starting complementary diet was 5 months. Prevalence of infant regurgitation, rumination syndrome and colic were 10.5%, 2.1%, and 0.6% while prevalence of infant dyschezia, functional constipation and diarrhoea were 0.9%, 1.1% and 0.2%. No subjects fulfilled criteria for cyclic vomiting syndrome. Breastfeeding infants were less likely to regurgitate, after adjusted for age, gender, ethnicity, birth weight and gestation (adjusted OR 0.23; 95% CI 0.10-0.51; p &LT; 0.001). For all other pFGIDs, there were no significant differences between various factors (gender, Malays vs. non-Malays, premature vs. term, birthweight of &LT; 2.5kg, 2.5-4.0kg and >4.0 kg).

Conclusion: Commonest pFGIDs in the study population is infant regurgitation, followed by infant rumination syndrome. The observed prevalence of all FGIDs are much lower compared to the prevalence reported in the literature (Ferreira-Maia AP et al. 2016).

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Increased prevalence of abdominal pain-functional gastrointestinal disorders in pediatric celiac patients despite a strict gluten free diet

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Objectives and Study: Recently, in 2016, the revised Rome IV criteria for the diagnosis of functional abdominal pain disorders (FAPDs) have been published. In adults, a recent meta-analysis suggest that patients with celiac disease (CD) have an higher risk of complaining symptoms compatible with irritable bowel syndrome (IBS) that might persist despite a strict gluten free diet (GFD). Few data are available in children. Aim of our study was to assess the prevalence of AP-FGIDs in a cohort of paediatric patients with CD after a long period of strict GFD.

Method: We studied 417 patients (62.83% Female) with a mean age of 13.7 years (range: 4.2-16 years) who were diagnoses as having CD according to ESPGHAN criteria on strict GFD for at least one year and with at least two consecutive negative celiac serological test. To assess the prevalence of FAPDs a revised Questionnaire on Paediatric Gastrointestinal Symptoms-Rome full respect of new Rome IV criteria was used. Three-hundred seventy-three children (45% female) with a mean age of 13.5 years (range: 4.3-20 years) enrolled among the closest, non celiac, sibling of the patient (or if no siblings available, the next child in kinship) were used as control.

Results: Considering the new Rome IV criteria, 48 children in the CD group and 25 children in the control group (6.70%) met criteria for a functional abdominal pain disorders [(11.5% vs. 6.7%; p &LT; 0.05); RR 1.57: CI 95%: 0.98-2.52)]. In particular, IBS was diagnosed in 30 as compared to 12 (7.2% vs. 3.4%; p &LT; 0.05; RR 2.3: CI 95%: 1.2-4.3), functional dyspepsia (FD) in 6 in both groups (1.4% vs. 1.6%; p = NS), and Functional Abdominal Pain not Otherwise Specified (FAP-NOS) in 7 as compared to 5 (1.9% vs. 1.3%; p = NS). Finally, the prevalence of constipation was higher in the CD group as compared to controls (39) [19.9% vs. 10.5; p &LT; 0.001; RR 1.9: CI 95% 1.4-2.7].

Conclusion: Patients with CD have an increased risk of developing a functional abdominal pain disorders, and in particular IBS and constipation despite strict adherence to a gluten free diet. Our results suggest that new strategies aiming at the management of IBS in celiac patients should be planned.

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Perception of school toilets and incidence of abdominal pain and constipation in elementary school in Germany

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Objectives and Study: Functional constipation and chronic abdominal pain are common features in the pediatric clinic. A suggested patho-mechanism is the refusal against painful and hard bowel movements and a vicious circle of hold back stool, hardening and colonic dilatation and further experiences of painful events. While toilet refusal syndrome is a known entity in toddlers, it is less described in school children. The aim of this study is to identify incidence of functional abdominal pain and constipation in elementary school and potential influences of perception of school toilets.

Methods: All elementary schools in the wider area of Giessen, a university town in the middle of hessia, north of Frankfurt, were contacted and asked to hand out questionnaires to children in the first 4 years of elementary school. The parents should answer basic questions about the perception of toilets and criteria of functional abdominal pain and constipation. The questionnaire was repeated after one year.

Results: From 1399 questionnaires deposited at eight elementary schools, only 277 could be retrieved (19.7%). From the second cohort 429 questionnaires could be retrieved (30.6%). While 212 (76.5%) families responded the child would use the school toilet for passing urine always, commonly or regularly (ACR), only 92 (33.2%) did so for passing stool. 46 (16.6%) were always disgusted by their school toilets, further 145 (52.3%) reported to be disgusted commonly or regularly. 106 (38.3%) parents answered their child would ACR avoid using the school toilet because of disgust. Retentive behavior was observed by 69 parents (25.0%) ACR, rarely by another 37 (13.4%). 126 parents reported their child would retain stool to avoid using the school toilet (45.5%). 138 (49.6%) parents answered their child would go directly to the toilet for bowel movement after school. 81 (29.2%) reported they remember soiling of stool. Children who were disgusted by and avoided using the school toilet showed significant higher prevalence of abdominal pain ACR (23.6% vs. 11.2%, p=0.0103)

The prevalence of functional abdominal pain as determined by questionnaire was 15.8%. While 9 parents knew their child suffered from constipation (3.25%), another 35 (12.6%) reported pain with bowel movement ACR, 89 (32.1%) hard bowel movements and 92 (33.2%) large diameter stool. 4 (1.4%) reported blood on the stool, 50 (18%) parents answered, their childs belly would be tender or bloated ACR.

Conclusion: Prevalence of abdominal pain and constipation is high in elementary school children and perception of school toilets with consecutive avoidance and retentive behavior could be an important influence.

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Asafoetida oleoresin gum with antimicrobial and antispasmodic activities is suitable for a novel method of controlling microbial overgrowth in paediatric patients with long-term gastro-jejunal feeding tube

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Background: Continuous increase in antibiotic resistance and antibiotic-associated diarrhoea caused by depleting commensal microbiota in the gastrointestinal (GI) tract warrant development of alternative methods to control small intestinal microbial overgrowth. Oleoresin gum obtained from Ferula asafoetida, a wild herb from Western Asia, has been traditionally used in many Eastern Countries for gastrointestinal problems including flatulence, parasite infection and abdominal cramps (antispasmodic); it has also been examined for antimicrobial activities. In this study, we have tested the antimicrobial properties of different asafoetida extracts against organisms commonly found in microbial overgrowth and evaluated the outcome of the use of asafoetida extracts in paediatric patients with gastro-jejunal tube.

Method: Food grade asafoetida powder was extracted with hot water, ethanol, hexane, ethyl acetate, heptane and xylene following standard protocol. Asafoetida powder in respective solvent was mixed well, and spun down. The supernatant was used to measure antimicrobial activities by disc diffusion method on agar media plates. Fresh liquid cultures of seven microbial strains were used. Antimicrobial activity was measured by the difference in zone of inhibition with asafoetida extracts vs. respective solvents as controls.

Case study: Two cases with history of recurrent bacterial overgrowth and Clostridium difficile infection warranted alternative therapy. First case (21 y) had spastic quadriparesis and was g-tube dependent. Second case (9 y) had Pitt-Hopkins Syndrome and gastrojejunostomy.

Results: Significant inhibitions of growth of Streptococcus pyogenes, Streptococcus mitis, Pseudomonas aeruginosa, and Candida albicans were obtained with different solvents extracts of asafoetida (Table 1). Maximum growth inhibition with aqueous extract was obtained against three bacterial strains Streptococcus pyogenes, Streptococcus mitis, Pseudomonas aeruginosa, and one fungal strain, Candida albicans. Limited growth inhibition was obtained for Staphylococcus aureus, and Klebsiella pneumoniae. None of the extracts inhibited growth of Escherichia coli. Bacteriostatic inhibition of growth with water extract was observed for Pseudomonas aeruginosa and Streptococcus pyogenes.

Case study report: Asafoetida cooking powder (1/8 tsp) in warm water was administered twice daily. Both tolerated the spice well. Further events of gas/flatulence/distension/eructation were alleviated for 4 and 3 months, respectively. Neither were capable of undergoing breath hydrogen testing.

Conclusion: Managing small bowel bacterial overgrowth remains a challenge. Antibiotic use generally results in resistant organisms and increases the risk of Clostridium difficile infection. We report a novel and effective use of an Ayurvedic herb extract renowned for its antispasmodic and antibacterial properties. We found Aqueous asafoetida extracts is more effective compared to organic solvent extracts against test organisms. Bacteriostatic activity of asafoetida extract may facilitate succession of beneficial commensal organisms in the GI tract. This may play an important role in reducing antibiotic resistance and maintaining microbiome diversity essential for a healthy GI tract. Longer term and larger studies are warranted.
Table 1: Difference in Zone of inhibition: Asafoetida extract vs respective solvent control (in mm)

<table>
<thead>
<tr>
<th>Extraction media</th>
<th><em>Streptococcus pyogenes</em></th>
<th><em>Streptococcus mitis</em></th>
<th><em>Escherichia coli</em></th>
<th><em>Klebsiella pneumoniae</em></th>
<th><em>Pseudomonas aeruginosa</em></th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Candida albicans</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Water</td>
<td>3.3 (± 0.7)</td>
<td>1.5 (± 0.15)</td>
<td>0</td>
<td>0</td>
<td>2 (± 0.54)</td>
<td>0</td>
<td>2 (± 0.67)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>2.7 (± 0.5)</td>
<td>1 (± 0.09)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hexane</td>
<td>1 (± 0.7)</td>
<td>1 (± 0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>2.5 (± 0.6)</td>
<td>1 (± 0.2)</td>
<td>0</td>
<td>1 (± 0.45)</td>
<td>1 (± 0.25)</td>
<td>5 (± 1.5)</td>
<td>1 (± 0.25)</td>
</tr>
<tr>
<td>Heptane</td>
<td>4 (± 1.0)</td>
<td>0</td>
<td>0</td>
<td>2 (± 0.7)</td>
<td>0</td>
<td>0</td>
<td>7 (± 1.5)</td>
</tr>
<tr>
<td>Xylene</td>
<td>1 (± 0.09)</td>
<td>0</td>
<td>0</td>
<td>1 (± 0.25)</td>
<td>3 (± 1.1)</td>
<td>1 (± 0.12)</td>
<td>1 (± 0.25)</td>
</tr>
</tbody>
</table>

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Duodenal Candida overgrowth and disaccharidases in children with Autism

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**Background and Study:** Gastrointestinal symptoms are common in children with autism. Candida overgrowth has been postulated as more common in these children. We reviewed our data on all children with Autism who underwent upper endoscopy for suspected gastrointestinal disorders.

**Method:** Following IRB approval retrospective chart review was conducted over a 5 year period. All patients had abdominal pain, gas, distension or diarrhea. First set had duodenal aspirates cultured and bowel flora identified. Subsequent samples were obtained from duodenal brushings and >1000 cfu/ml was identified as Candida Overgrowth. Disaccharidases and mucosal histology was also reviewed. Age and gender matched control patients (double sample size) were randomly selected for comparison.

**Results:** Table 1 presents flora identified in Autistic children and controls in the initial phase. Subsequently 1000 cfu/ml was chosen as the cut off. With duodenal brushings, 6/38 with autism and 1/85 controls had Candida overgrowth at 1000 cfu/ml or greater (P< 0.005). The one control patient had asthma and was on oral and inhaled steroids. Duodenal histology changes under light microscopy did not show any association. Disaccharidases with any abnormality including lactase deficiency did not show any association.
Discussion: Candida was identified twice as often on duodenal aspirates in children with Autism and GI symptoms compared with controls. When using a 1000 cfu/ml cut off, higher prevalence of candida in children with Autism was also seen compared with, than age and gender matched controls. Duodenal histology, and disaccharidases did not differ between the groups. Overall, though increased, candida overgrowth is not common in children with autism with only 13 % having >1000 cfu/ml.

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G-P-218

Piecemeal deglutition and the implications for pediatric pressure impedance swallow assessments

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Objectives and Study: High resolution impedance manometry (HRIM) enables biomechanical swallow assessment and to date has focused on analysis of single swallow selection following oral administration of a bolus. Piecemeal deglutition (PD), is defined as swallowing a single bolus in two or more portions in order to clear the oral cavity. PD is a common feature in pediatric swallowing and the ability to discriminate between saliva and bolus swallows is paramount during manometric swallow assessments. Therefore we investigated swallow selection from PD sequences using HRIM to ascertain the impact on contractility, distension and flow timing swallow function measures.

Method: Pharyngo-esophageal motility and bolus flow were assessed in 27 children (19M, mean age 15 months) with repaired esophageal atresia and trachea-esophageal fistula, but who were asymptomatic of oropharyngeal dysphagia, as ethical considerations protect healthy children from invasive testing. These children were considered suitable, as pharyngeal swallow patterns were adventitiously captured during their investigations. A consistent volume of between 2 - 5 ml saline boluses were given to each patient, and PD sequences were defined based on the number of swallows required to clear the bolus from the oral cavity: pattern A = 1-2 swallows; pattern B = 3 swallows; and pattern C = 4+ swallows. Admittance curves (inverse of impedance) were used to detect bolus vs saliva swallows. The largest bolus volume swallowed was noted as the dominant swallow in each pattern. Pressure Flow Analysis was used to define contractility, distension and flow timing metrics. Data were averaged for each PD pattern, and compared with dominant swallows from each pattern.

Results: PD pattern B (43.7%) was most prevalent across the cohort. Age related differences were noted in some swallow function variables: hypopharyngeal intrabolus pressure was higher (p<LT; 0.05), UES relaxation pressures were lower (p&LT; 0.001), UES opening diameter was wider (p&LT; 0.001) and distension-contraction latency was longer (p&LT; 0.05) amongst older children compared to infants. Differences in UES distension and pharyngeal flow timing measures were see in relation to age and PD pattern type, whereby a larger pharynx in older children, and a larger bolus as with fewer PD swallows elicited greater distension (p&LT; 0.005) for a longer latency (p&LT; 0.05).

Conclusions: HRIM can be performed in infants and young children and enables clear observation of swallow motor patterns. PD reduces bolus volume, and biomechanical swallow measures are impacted. Therefore it is necessary to consider PD for accurate pediatric HRIM analysis and interpretation. Selection of dominant bolus swallows from a PD sequence provide swallow profiles which best represent a child’s swallow function.

Disclosure of interest: Please consider this abstract although it was presented at ESSD 2017. The ESPGHAN guidelines do not specify congress presentation until final submission page. T Omari & N Rommel - Inventorship of Australian Patent 2011301768 which covers the analytical methods described. T Omari - Copyright over AIMplot software. All other authors have no conflicts of interest to disclose.

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Is it infant colic? Or early symptom of autistic spectrum disorder?

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Objectives and Study: Gastrointestinal disorders (GI) are common in autistic spectrum disorder (ASD). Infant colic (IC), the functional GI disorder of infancy, has not been evaluated in this patient group. The aim of this study is to determine the rate of IC in ASD and investigate a possible association between ASD and IC.

Method: The study group included patient group (ASD) and healthy controls. The parents were questioned with Diagnostic Criteria for Infant Colic for clinical research purposes defined in Rome IV to diagnose IC, retrospectively. The sample size was estimated by considering a maximum type I error probability of 5% (alpha) and a type II error of 20%.

Results: The study consisted of 100 ASD patients (mean age: 6.6±3.5 years) and 100 healthy controls (mean age: 5.3±2.8 years). The rate of IC was 16% and 17% in ASD group and control group, respectively (p>0.05). A group of infants with excessive crying was observed with late onset, long duration and was described as persistent crying infants. The rate of persistent crying infants was significantly higher in ASD group than controls (32% vs 9%, p<LT; 0.001). The relative risk of persistent crying was 4.40 in ASD. The rate of being misdiagnosed as IC in this group was 78%.

Conclusion: The rate of IC is not increased in patients with ASDs. But infants with excessive crying should be well evaluated before being diagnosed with IC. Especially late onset and long duration of an infant crying may be a risk factor for developing ASD.
Gas reflux in children: there is connection with cow's milk allergy?

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Objectives and Study: Multichannel intraluminal impedance (MII) recording allows the assessment of flow through the oesophagus and the differentiation between liquid and gas contents. We aimed to evaluate the role of gas reflux in children evaluated with pH-metry associated with MII (MII-pH).

Method: We performed a retrospective study, examining all of our recordings of patients suspected of gastro-oesophageal reflux (GOR) evaluated with MII-pH and selected the ones with pathological gas reflux. The cut-off value for pathological gas reflux was 72. The following parameters were evaluated: reflux index, the number of acid reflux episodes detected with pH-metry, the total number of reflux episodes detected by impedance, the number of acid reflux episodes, the number of weakly acidic reflux episodes, the number of weakly alkaline reflux episodes and the composition of the reflux: liquid, mixed or gaseous.

Results: Thirty two children (18 male) were selected for the study, according to protocol, aged between 4 months and 16 years (mean age 3 years and 5 months). Using MII, 3586 gaseous reflux episodes and 3970 liquid and mixed reflux episodes were identified. Predisposing conditions for gaseous reflux were identified in 24 children: 20 children were diagnosed with alimentary allergies: one with numerous food allergy and 19 with cow's milk allergy (17 non IgE mediated allergy) and four children with small intestinal bacterial overgrowth detected with glucose breath test. 11 patients were treated with proton pump inhibitors for pathologic acid GOR.

Conclusion: MII permits the detection and characterization of GOR, including gaseous reflux. The majority of children with gaseous reflux in our study were allergic (62.5%).
The role of combined multichannel intraluminal impedance and pH oesophageal testing in children suspected of gastro-oesophageal reflux with normal pH-metry

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Objectives and Study: A retrospective study was performed in order to evaluate the results of multichannel intraluminal impedance (MII) testing and its therapeutic implications in children suspected of gastro-oesophageal reflux (GOR) with normal pH-metry.

Method: For patients suspected of GOR, without anti-reflux treatment, examined through pH-metry associated with 24h multichannel intraluminal impedance (MII-pH) and with normal pH-metry (differently defined according to age), the following were analysed: the number of weekly acid reflux (WAR) episodes, the number of weekly alkaline reflux (AlkR) episodes, the symptomatic correlation between reflux and symptom by analysing the probability of symptomatic association (SAP), the extension of reflux episodes within the level of proximal oesophagus recorded in percentage.

Results: 27 children (15 male, 12 female), age between 1 month and 11 years (19 infants), were recorded. The reasons for recommending pH-metry associated with electrical impedance were recurrent vomiting and growth failure in 14 cases, recurrent wheezing associated with chronic vomiting in 7 cases and recurrent wheezing or chronic cough in 6 cases. All patients showed in most cases an extension of the reflux episodes at a proximal oesophagus level. WAR was increased in the case of 16 children, 8 positive symptomatic correlation positive (4 with acid reflux) and 4 increased WAR as well as positive symptomatic correlation. AlkR episodes were absent in all children. The therapeutic recommendations were: hypoallergenic diet in 9 cases, prokinetic agents and/or alginates for 19 patients and histamine 2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) in 8 cases.

Conclusion: The association of electrical impedance to pH-metry provides new criteria in establishing pathological GOR diagnosis, and allows an accurate therapeutic approach in the case of these children.
Are the mathematical formulas based on the size suitable for the calculation of the position of esophageal pH monitoring?

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Objectives and Study: The place where the esophageal pH-electrode is placed in the esophagus, influences the accuracy of the esophageal pH and the impedance monitoring (IM). The gold standard for the location of the lower esophageal sphincter (LES) is the esophageal manometry but, in clinical practice, the guides recommend placing the esophageal pH-electrode two vertebral bodies above the diaphragm. There are several mathematical formulas to predict the distance from the nose where the pH-electrode should be placed according to the patient’s size or length. We intend to study the prediction ability of these formulas.

Method: Since August 2016 we collect prospectively and consecutively the data of the patients who had undergone a 24 hours, pH and impedance monitoring (IM). The position of the pH or IM probe was calculated with fluoroscopy in all cases, using as a reference the recommended position according to the guidelines. The nose-electrode distance and the anthropometric data of each patient were recorded. The distance predicted by Nowak, Strobel, Staiano-Clouse and Moreau’s mathematical formulas was simulated in a specially designed spreadsheet. Subsequently, the difference between the real distance and the approximate distance was calculated. Success was defined as a difference less than 1/12 of the length of the thoracic spine estimated by Currarino’s formula.

Results: A total of 82 patients were included, ages ranging from 2 months to 19 years old. Nowak’s formula obtained the highest success rate: 67.1% (95% confidence interval -95%CI- 56.9% to 77.2%). GOSH table achieved a poorer performance and got 53.7% (95%CI 42.9% to 64.5%) of final probe position right. Staiano-Clouse, Strobel and Moreau’s formulae correctly predicted less than 25% of cases. Pearson’s correlation coefficient for Nowak’s formula was calculated in 0.95. Absolute difference between predicted and real probe length form nose was 1.6 cm on average (95%CI 1.3 to 1.9). We did not observe neither constant nor proportional deviations through the Passing-Bablok method. However, a tendency towards a constant error of -1.5 cm was found, but nevertheless we did not manage to improve its success rate when trying to correct the formula. The analysis of the different age and sex groups did not establish a particular patient profile with a higher error risk

Conclusion: Nowak’s formula is the most accurate mathematical formula to predict where to place the esophageal pH and impedance monitoring: distance from nose to oesophageal pH electrode (cm) = 3.2 + 0.2 x height (cm). Nonetheless, its accuracy is not perfect and therefore, in more than a third of children, initial estimated setting should be corrected by radiography.

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Epidemiology of gastroesophageal reflux disease in children: a systematic review

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Objectives and Study: Gastroesophageal reflux (GER) is defined as GER disease (GERD) when causing troublesome symptoms or complications. In this study we aimed to review the literature regarding the incidence and prevalence of GERD in children aged 0-21 years.

Methods: Databases of PubMed, EMBASE and Cochrane were searched from inception to November 22, 2016. English-written studies based on birth cohort, school based or general population samples were included. Quality assessment was performed using a purpose-designed tool. Due to large heterogeneity in study population and methodology, no meta-analysis was performed.

Results: In total, 3214 unique studies were found, of which 18 studies were included. Six studies reported data on GER and 12 on GERD. Reported GER prevalence was up to 86.9% in infants and tended to decrease with increasing age in the first months of life (Figure 1). GERD prevalence varied widely amongst studies, ranging from 0.18 to 35% depending on definition used and age-group studied. Cumulative incidence of GER ranged from 22% to 63% in premature infants. Incidence of GERD was found to be 0.91 per 1000 person-years in infants and children, and ranging from 0.47 per 1000 person-years in a sample of males up to 2.26 per 1000 person-years in a sample of females.

Conclusion: Giving a true estimate of the worldwide extent of paediatric GERD was hampered by the lack of application of a uniform definition of GERD in the absence of a well-validated diagnostic tool. True estimates of the extent of GERD will allow a better understanding of what is normal and abnormal and may enhance the usability of research findings for clinical practice and better patient care. Therefore, there is a need for global consensus on a, symptom based, definition of paediatric GERD.
The prevalence of GER and GERD in infants and children aged 0 to 21 years

Figure 1. ▲, study on GER; ●, study on GERD. The bars in the graph indicate the age range of the study population (mean ages within this range not provided). The zoomed detail on the prevalence of GER in infants shows the observed trend towards a decrease in reported GER prevalence rates during infancy. GERD prevalence seems to increase during adolescence.

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The role of multichannel intraluminal impedance - pH testing in the clinical management of children with gastro oesophageal reflux disease

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Objectives and Study: Limited data exist on the impact of combined multichannel intraluminal impedance-pH (MII-pH) testing in the clinical management of children with gastro oesophageal reflux disease (GORD). The aims of our study were to determine whether MII-pH testing led to a change in the medical and surgical management of children with GORD and to evaluate the diagnostic yield of MII-pH testing over pH monitoring alone.

Methods: Retrospective chart review of all patients who underwent MII-pH testing at Sydney Children's Hospital between 2008 and 2016. Changes in prescribed anti-reflux medications, referral for anti-reflux surgery and alterations in feeding plan were evaluated. Differences in medical, surgical and feeding outcome in terms of the characteristics of the cohort were compared using Fisher's exact test (< 5 patients) and Pearson Chi-square test (> 5 patients).

Results: Our study included 365 patients, 260 (71.2 %) of whom were on acid-suppressing therapy during MII-pH testing. The median age was 6 ± 5 years, 205 (56%) were males, 83 (22.7%) were < 1 year of age and 304 (83.3%) were orally fed at the time of testing. The majority of patients (98.6%) presented with typical oesophageal symptoms, 54.5% had extra oesophageal symptoms and 53.2% had both. 150 children (41%) had comorbid conditions of which 21.6% had neurological impairment, 18.6% had oesophageal atresia and 0.8% had cystic fibrosis. MII-pH testing was considered to be abnormal when patients were found to have abnormal acid reflux, abnormal retrograde bolus movements (RBMs) and hypersensitive oesophagus. Acid reflux was present if patients had an abnormal acid reflux index. Classification of abnormal RBMs was made if patients aged < 1 had >100 RBM episodes in a 24-hour period or those aged ≥ 1 year had >70 RBM episodes. Hypersensitive oesophagus was present if patients had a normal acid reflux index and RBMs but positive symptom association. Based on these definitions, 72.1% of patients had abnormal MII-pH results. On multivariate analysis, infants were significantly more likely to have abnormal MII-pH results compared to older children (p=0.045). Overall, 17.5% of patients had abnormal acid reflux, 8.2% had abnormal RBMs and 46.3% had hypersensitive oesophagus. MII-pH testing increased the diagnostic yield of GORD by 54.6% compared to pH testing alone. Results of MII-pH testing led to medication changes in 44.7% of patients (Table 1) and referral for anti-reflux surgery in 6.8% of patients.
| Type of symptom (oesophageal or extra oesophageal), endoscopy results and presence of comorbidities had no significant association with MII-pH results. A greater proportion of patients with abnormal RBMs (16.7%) were referred for anti-reflux surgery compared to other diagnoses. Alterations were made to the feeding plan of 8.2% of patients. Neurologically impaired patients and infants with abnormal MII-pH results were significantly likely to have changes in their mode of feeding (p=0.001).

**Conclusions:** MII-pH testing is clinically useful in the management of children with GORD and over half the patients had changes to their medical treatment, feeding plan or surgical referral based on the results of MII-pH testing. MII-pH testing increased the diagnostic yield by 54.6% among symptomatic children with GORD over pH monitoring alone.

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Beck Depression Inventory scores in adolescence with functional gastrointestinal disorders

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**Objectives and Study:** In recent years, there is an increasing interest to the topic of emotion regulation as disorders, psychopathology mechanism of various psychological problems, and also as the main target of treatment. In various gastrointestinal system diseases, emotional dysregulation reduces pain tolerance and increases the severity of the disease. In the clinic, drugs that regulate emotional mood have been shown to reduce the severity of the disease. Depression is one of the major mental health problems of adolescence. Although the incidence of depression is less than 3% in childhood, this rate increases to 14% in adolescence. Increased emotional dysregulation during the adolescence period causes gastrointestinal symptoms to be more frequent and severe. In this study, Beck Depression Inventory scores were investigated in patients admitted to our clinic with functional gastrointestinal disorders.

**Method:** According to Rome IV criteria, 200 patients with functional abdominal pain and dyspepsia aged 12-18 years were included in this study. 100 patients without a chronic disease were taken as control group. Patients completed the self-report questionnaires about symptoms, school performance, nutrition and sports habits. We used Beck Depression Inventory -II (BDI-II) to assess the patients' depression.

**Results:** The mean age of study group was 15.29±1.48 years (Range 12-18 years), median 16 years; 80% (160/200) were girls. The mean age of control group was 14.96±1.66 years (Range 12-17 years), median 15 years; 70% (70/100) were girls. There is no difference between the two groups for age and gender (Table 1). A significant difference was observed in Beck Depression score between study and control groups. (Table 1). No difference was found in nutrition and sports habits between two groups. A significant difference was seen in school performance between two groups (p< 0.001) in the study groups, 112 (56%) children had 'very well' school performance, whereas 24 (24%) children in the control group were 'very well'.

<table>
<thead>
<tr>
<th></th>
<th>Study group Median(Min-Max)</th>
<th>Control grup Median(Min-Max)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>16 (12-18)</td>
<td>15(12-17)</td>
<td>0.133</td>
</tr>
<tr>
<td>Beck Depression Score</td>
<td>12.5(0-53)</td>
<td>10.0(0-41)</td>
<td>0.014</td>
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</table>

**Conclusion:** Functional gastrointestinal disorders (FGIDs) are variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. The frequency is increasing steadily. Several studies have shown that these disorders create physiological and psychological stress and lower quality of life. Especially they are common in the adolescent age. Emotional dysregulation has been shown to be the cause of many clinical behaviors and psychological problems. In adolescents, this emotional dysregulation is more intense. Especially the depression frequency is higher in this age group and these patients believe that their health is poor. There is also an inverse relationship between the degree of depression and the point of view of health. In conclusion, it is not clear that emotional dysregulation induces FGIDs or FGIDs cause emotional dysregulation. But it is known that these diseases are common in the adolescent age group and mood stabilizers are useful in treatment.

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Multichannel impedance monitoring for distinguishing non-erosive reflux esophagitis with minor changes on endoscopy

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Objectives and Study: There are reports about the relationship between baseline impedance level and esophageal mucosal integrity by endoscopic findings such as erosive and non-erosive reflux esophagitis. However, many children with symptoms of GORD have normal findings or minor changes on oesophagogastroduodenoscopy (OGD). We would like to examine whether trivial changes in OGD study can be evaluated by multichannel Impedance monitoring as an alternative measure.

Method: Patients (ages 0-18 years) with symptoms related to GOR who underwent OGD and pH-MII monitoring in Women’s and Children’s Hospital in Adelaide, Australia, between 2014 and 2016 were retrospectively studied and the following data were collected: demographics (age, gender), pH-MII data (acid exposure (pH), included reflux index (acid exposure time), mean acid clearance time, longest episode of acid exposure). Impedance data included: the number of acid and non-acid reflux events, and baseline impedance (distal channels; 5,6 was objectively calculated using software created using Matlab (MathWorks, Natick, MA)). Endoscopic findings were classified by modified Los Angeles grading, LA-N as normal, LA-M as with a minimal change such as the reddish or whitish mucosa, or friability in the mucosa. Patients on proton pump inhibitors were excluded. Other exclusions were the presence of esophageal anatomical anomaly, eosinophilic esophagitis, and previous anti-reflux surgery.

Results: Seventy patients (43 boys, 61%) were enrolled with a mean of age of 7.9 years (range: 10 months to 17 years) in this study. Fifty-one patients (72.9 %) were allocated to LA-N, while LA-M evident in 19 patients (27.1%). Statistical differences were observed in three parameters: frequency of non-acid reflux (p=0.022), baseline impedance in channel 5 (p=0.024), and 6 (p=0.005). The mean values ± SD of the data were LA-N: 21.9 ± 16.2 episodes, 2574.8 ± 697.0 Ω, 2491.1 ± 780.4 Ω, in LA-M: 40.4 ± 31.4 episodes, 2163.2 ± 569.7 Ω, 1897.3 ± 737.7 Ω.

Conclusion: In children with GOR, minor esophageal endoscopic findings were associated with lower baseline impedance. It is therefore reasonable to relate the number of non-acid reflux episodes to minor changes in the distal esophagus.
Objective: To determine whether a non-pathologic esophagogastroduodenoscopy (EGD) and reassurance improves the quality of life (QoL) of children and families, in paediatric patients with abdominal pain-related functional gastrointestinal disorders (FGIDs).

Study: Abdominal pain-related FGIDs are common among children and adolescents. Abdominal pain, defined as a functional disorder, with no organic cause to account for, brings much anxiety and distress to patients and their families and has significant impact on daily function and QoL. The study aimed to explore the impact of normal EGD examination on QoL of children, and on parents’ perception of the child's condition. QoL in patients were compared before and after endoscopy and report of absence of disease to patients and family.

Methods: The study recruited children/adolescents aged 8-18 years fulfilling ROME III criteria for abdominal pain-related FGIDs and referred to EGD by the paediatric gastroenterology specialist. Prior to EGD procedure, both parent and child filled the PedsQL4.0 form, a reliable and validated paediatric QoL questionnaire. The patients and their parents were informed immediately after the procedure about the macroscopic findings. Additional QoL surveys (PedsQL4.0 questionnaire) were performed 1 month after EGD and 1 and 2 months after the pathology report was communicated to families. Children with pathologic findings on EGD or biopsies, considered to be the cause of patients’ complain were excluded from the study. Friedman test followed by Wilcoxon sign rank test were used for pairwise comparisons of the QoL parameters at baseline and different time points after EGD. The study was conducted in conformity with local IRB regulations and written informed consent was obtained from all the participants' parents/legal guardians before enrollment.

Results: The study included 48 patients, age 14.3±2.5 years, 73% females. There was a significant change in child’s QoL score calculated for the 4 time points; baseline, 1 month after EGD and 1 and 2 months after the pathology report was revealed (Mean±SEM: 26.7±1.9, 21.7±2.2, 17.3±2.1 and 16.1±2.3 respectively, \( P<0.0001 \)). For the same time points a significant improvement in QoL score was also indicated by analysis of parents’ questionnaires (27.4±2, 17.9±2.4, 14.1±2 and 13±1.8 respectively, \( P<0.0001 \)) (fig. 1). No association between the change in the child’s QoL score and age, gender, or parents’ education was found.
Fig 1. Mean quality of life score of every PedsQL4.0 survey components was calculated for 4 time points (mean+SEM, n=48). Score is inversely proportional to quality of life. Differences between 4 time points were compared using Friedman test followed by Wilcoxon sign rank test with Bonferroni correction for pairwise comparisons. Statistical values compared means for each time point with its previous (*p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001, ns-not significant).

Conclusions: In this study, normal EGD examination, as a definite/additional proof of the absence of disease as the cause of abdominal pain, improved the QoL of paediatric patients with FGIDs and their parents. The study suggests that within the framework of the biopsychosocial model of FGIDs the psychological component may play a significant role, at list in some of the patients.

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**GASTROENTEROLOGY - GI motility, GERD and functional GI disorders**

G-P-228

**Gastric emptying of solids in children measured with the $^{13}$C-octanoic acid breath test: isotope ratio mass spectrometry compared with non dispersive infrared spectrometry for analysis of breath samples**

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**Objectives and Study:** $^{13}$C-octanoic acid breath test ($^{13}$C-OBT) is used to measure gastric emptying (GE) of solids. Analysis of breath samples for $^{13}$C-enrichment is performed using isotope ratio mass spectrometry (IRMS) or non dispersive infrared spectrometry (NDIRS). NDIRS is cheaper and easier to perform than IRMS. The aim of this study was to measure GE of solids in children with the $^{13}$C-OBT comparing IRMS and NDIRS.

**Method:** GE of a standardized pancake test meal was measured with $^{13}$C-OBT in children with upper gastrointestinal (GI) symptoms suggestive for delayed GE. Two breath samples were collected at baseline and then every 15 minutes for 240 minutes in center A (UZ Brussel). The breath samples were analyzed respectively with NDIRS in center A and with IRMS in center B (UZ Leuven). Gastric half emptying time ($t_{1/2}$-GE) was calculated using the Ghoos method with NDIRS in center A and IRMS in center B. GE was defined as normal or delayed according to NDIRS reference values from center A and IRMS reference values from center B which were established previously for the same pancake test meal. Cohen's $\kappa$, mean error and 95% limits of agreement of Bland-Altman plots (of GE NDIRS - GE IRMS) were calculated using R version 3.1.2. A p-value < 0.05 was considered statistically significant.

**Results:** A total of 42 children (57.1% girls) were included: mean age (SD) was 10.0 (3.7) years and median (Q1;Q3) BMI z score was 0.23 (-0.95;1.1). Median (Q1;Q3) $t_{1/2}$-GE for NDIRS was 153.5 min (137.3;186.5), which was not statistically, nor clinically different ($p=0.083$) from the median (Q1;Q3) $t_{1/2}$-GE for IRMS (164.5 min (143.3;190.3)). The correlation between both techniques was strong ($p=0.81$; p&LT; 0.001). The mean difference (95% CI) between both techniques was -12.8 min (-97.5;71.9) with a lower limit of agreement (LOA) of -97.5 min and an upper LOA of 71.8 min. This variation seemed largely due to the presence of 4 outliers (2 of them considered delayed GE by both techniques). The mean difference between NDIRS and IRMS without these outliers was -0.5 min (95% CI -5.4;4.4) with a lower LOA -29.7 min and an upper LOA of 28.8 min.

There were 8 (19.0%) children with a delayed GE from the NDIRS group using NDIRS references, but 14 (33.3%) children with a delayed GE from the IRMS group using IRMS references. However, there were only 9 (21.4 %) children with delayed GE from the IRMS group when NDIRS references were used. In analogy, there were 12 (28.6 %) children with delayed GE from the NDIRS group when IRMS references were used. The $k$-value for the comparison of the outcomes of both tests was moderate (0.52 (95% CI 0.22;0.83); p&LT; 0.001). When the same references were used for all tests, the $k$-value increased to (0.63 (95% CI 0.32;0.94); p&LT; 0.001) for NDIRS references and (0.78 (95% CI 0.56;0.99); p&LT; 0.001) for IRMS references.

**Conclusion:** Both techniques appear to measure comparable gastric half emptying times in children with upper GI symptoms; the outcomes tied to both techniques differed however substantially. This seems to be related to the reference values that are used. The clinical significance of the small group of outliers needs to be determined in a larger study population. Uniform reference values are required for GE in children.

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Anterior cutaneous nerve entrapment syndrome in children - prospective observational study

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Objectives and Study: Anterior cutaneous nerve entrapment syndrome (ACNES) is defined as an abdominal wall neuralgia characterized by localized abdominal pain due to entrapment of cutaneous terminal branches of intercostal nerves (TH7-TH12) penetrating the rectus abdominis muscle. Although ACNES can be simply diagnosed, it is often an overlooked cause of abdominal pain. Abdominal pain is usually considered to be visceral while the abdominal wall, as an origin of the pain is rarely considered. Therefore, children often undergo inappropriate investigations and unsatisfactory treatment leading to a substantial increase in healthcare costs. Data for pediatric patients, especially regarding the treatment modalities are scarce. The aim of this study is to present a treatment modality of ACNES with combined local subfascial anesthetic and corticosteroid injection in a prospectively collected cohort of pediatric patients.

Method: This was a prospective observational long-term study, which included pediatric patients who were diagnosed with ACNES in a tertiary care pediatric center and followed up for at least 12 months (median 1.7 years, range 1-2.7 years). All children were treated by ultrasound guided subfascial injection of 40 mg 1% lidocaine and 4 mg dexamethasone into the rectus abdominis muscle in the place of the most severe pain (trigger point infiltration).

Results: The study included 38 children (28, 73.7% female; median age 15 years). The majority of patients had pain in the lower right abdominal quadrant and were diagnosed in a median of 6 (range: 0.5 to 50) months after symptoms started. Overall, 24 (63%) patients achieved sustained symptom-free remission after a median of 1 (mean 1.6; range: 1 to 5) trigger point infiltrations during the first treatment session. Five (13%) children were surgically treated due to a lack of long-term response. Children who were surgically treated required a higher number of block applications during the first session of treatment, compared to children who were successfully treated conservatively. There was no difference in gender, age, BMI Z score, pain location, duration of symptoms prior to diagnosis, or number of block injections initially applied in children who were in pain-free remission compared to children who required repeated injections during the first year.

Conclusion: ACNES in children can be successfully treated by a combined local subfascial anesthetic and corticosteroid trigger point infiltration. Importantly, as shown here, correct diagnosis can lead to successful treatment in the majority of patients.

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Bladder problems in children with functional defaecation disorders: a systematic review

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Objectives and Study: Bladder problems, like lower urinary tract symptoms (LUTS) and urinary tract infections (UTI) are often reported in children with functional defaecation disorders. The extent of the problem is unknown. The international Children's Continence Society has introduced the term Bladder and Bowel Dysfunction to emphasize the frequent combination of bladder and bowel problems. The aim of this study is to systematically review the prevalence of bladder problems in children with functional defaecation disorders and to compare this prevalence rate among children with and without functional defaecation disorders.

Method: A literature search was conducted in Medline, Embase, PsycINFO and Cochrane library. Studies investigating the prevalence of bladder problems in children aged 4 to 17 years with functional defaecation disorders were identified. There was no language restriction. Two reviewers independently extracted data, and assessed study quality with a checklist for prevalence studies. Prevalence rates of bladder problems in children with FDD were extracted or calculated. Relative risks were calculated to compare the prevalence of bladder problems between children with and without FDD. Clinical heterogeneity between the individual studies was investigated in order to determine whether a pooled meta-analysis of the reported prevalence rates and relative risk would be appropriate and meaningful.

Results: Among 23 studies of children with FDD, 22 reported the prevalence of LUTS (12,281 children) and 7 reported the prevalence of UTI (687 children). LUTS (combined symptoms), LUTS (individual symptoms), and UTI had prevalence rates of 37%-64%, 2%-47%, and 6%-53%, respectively. The relative risks were 1.24-6.73 for LUTS (20 comparison LUT symptoms) and 2.18-6.55 for UTI (2 comparison studies), but the 95% confidence intervals indicated non-significance in 6 and 2 studies, respectively. Due to clinical heterogeneity in definition of FDD, definition of LUTS, and clinical setting a meta-analysis of the reported prevalence and relative risks would be inappropriate and meaningless.

Conclusion: Bladder problems seem common in children with FDD, but the reported prevalence varies greatly. Comparison studies suggest that children with FDD are more likely to have bladder problems than children without FDD. We recommend that clinicians be aware of concomitant bladder problems in children presenting with FDD. Constipation management (by laxatives) and urotherapy are recommended for the treatment of combined non-neurogenic bladder and bowel dysfunction in children.
Quality of life in Allgrove syndrome and isolated esophageal Achalasia in children, in- long-term follow-up

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Objectives and Study: Esophageal achalasia (EA) is a primary disorder of esophageal motility. The disease is rare in children younger than 15 years old. The aim of the study was to analyze the clinical presentation, treatment outcome and quality of life (QOL) of isolated Achalasia (IEA) and in patients with Allgrove syndrome (AS) before treatment and at present.

Method: We performed analysis of disease course and management in EA- IEA and AS. Symptoms questionnaire with questions about symptoms before treatment and at present was sent to all patients. Moreover, we assessed QOL patients with EA using Urbach questionnaire (UQ), which is validated questionnaire for EA. In UQ minimum score is 10 which means good QOL and maximum score is 31 - bad QOL.

Results: Sixty patients with EA (26 F and 34 M), including 9 patients with AS were enrolled to the study. The median age at diagnosis was 12.01 yrs (1.36 - 17.63). Among them, 9 patients, with AS, in the middle age 7.85 yrs at the time of EA diagnosis, were distinguished. Mean time from the first symptoms to diagnosis was 1.86 yrs (range 0-10.98). Mean time of follow up was 11.63 yrs (range 0.75-26.18). Before treatment, most of the patients, 30/58 (52%) tolerated fluid diet (25/29 [51%] vs 5/9 [56%], respectively), whereas 32/46 (70%) tolerated normal with need to sipping (28/38 [74%] vs 4/8 [50%], respectively) after treatment. In the questionnaire, 44/46 (96%) of patients reported symptoms of disease at diagnosis (37/38 [97%] patients with IEA and 7/8 [87.5%] patients with AS). After treatment symptoms were observed in 14/46 (30%) patients (11/38 [29%] vs 3/8 [37.5%], respectively). At baseline, dysphagia was reported in 39/46 (85%) patients (33/38 [87%] patients with IEA and 6/8 [75%] patients with AS); regurgitation, in 42/46 (91.5%) patients (35/38 [92%] vs 7/8 [87.5%] respectively); heartburn, in 10/46 (22%) patients (10/38 [26%] and 0/8, respectively); chest pain, in 22/46 (48%) patients (20/38 [53%] and 2/8 [25%], respectively); cough and chocking, in 17/46 (37%) patients (15/38 [39%] and 2/8 [25%], respectively). After treatment, dysphagia was reported in 9/46 (20%) patients (7/38 [18.5%] patients with IEA vs 2/8 [25%] patients with AS); regurgitation in 5/46 (11%) patients (5/38 [13%] vs 0/8, respectively); hartburn in 6/46 (13%) patients (6/38 [16%] vs 0/8, respectively); chest pain in 4/46 (9%) patients (4/38 [11%] vs 0/8, respectively); cough and chocking in 4/46 (9%) patients (3/38 [8%] vs 1/8 [12.5%], respectively). The differences were statistically significant despite heartburn. Fifty (83%) patients were treated surgically, among them 22 (44%) before the procedure were treated endoscopally (pneumatic dilatation procedure - PD) vs 28 (56%) treated only surgically (Heller myotomy - HM). Six patients were treated only endoscopically (PD). According to UQ, the best QOL had patients treated by PD before surgery (mean 15.7 point; median 15), then patients treated only by HM (mean 16.4 points; median 17) and the worst patients treated by PD only (mean 20.3 points; median 20).

Conclusion: Heller myotomy with previous pneumatic dilatation procedure should be the procedure of choice for treating EA in children with the best QOL. Any of therapeutic procedures not guarantee resolution of symptoms in long term follow-up.

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Nutrient fortification of milk prolongs intestinal transit time without effects on gastric emptying rate in preterm piglets

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Objectives and Study: Human milk fortifiers (HMFs) are commonly added to mother’s own milk (MM) and donor human milk (DM) to secure optimal growth of preterm infants. When to initiate fortification is unclear and there are concerns of feeding intolerance defined by eg. delayed stomach emptying as well as constipation, abdominal distension and necrotizing enterocolitis (NEC) after adding HMF. We used preterm piglets as a model for preterm infants to investigate how nutrient fortification of bovine milk with protein-rich bovine colostrum, would affect gut motility the first weeks after birth.

Method: Piglets were delivered by cesarean section at 90% gestation and block randomized into two groups fed either increasing volumes of dilute bovine milk (CONT, n=22), or dilute bovine milk fortified with bovine colostrum powder (FORT, n=16) for 19 days. Total protein contents were 27g/L (CONT) and 55 g/L (FORT). Food passage time was evaluated by stomach-intestine-colon contrast examination using serial x-ray imaging.

Results: On day 4, at enteral feeding volumes of 96 mL/kg/d, the stomach emptying time, intestinal transit time, and time to reach from caecum to rectum, were similar between CONT and FORT. However, on day 18, with enteral feeding volumes of 180 ml/kg/d, intestinal transit time were longer in FORT (2.69 ± 0.31 hours) piglets relative to CONT (1.57 ± 0.16 hours)(p< 0.05), while stomach emptying time, and colon transit time, were similar between groups.

Conclusion: Results indicate that fortification of milk with bovine colostrum prolonged intestinal transit time on day 18 without effects on gastric emptying or colon transit time. Fortification with bovine colostrum will unlikely increase feeding intolerance defined by eg. stomach emptying in preterm neonates, and prolonged intestinal transit time may allow more time for nutrient absorption. Examination of food transit time by stomach-intestine-colon x-ray contrast examinations is a feasible method to investigate factors influencing gut motility and feeding intolerance in preterm neonates.

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Micronutrient status and the effect of a low FODMAPs diet in children with irritable bowel syndrome

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Objectives and Study: A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) often is used to manage functional gastrointestinal symptoms in patients with irritable bowel syndrome (IBS), yet there is limited evidence of its efficacy in nutritional status. We investigated micronutrient status in a group of children with irritable bowel syndrome (IBS) and the effects of a diet low in FODMAPs in their micronutrient status.

Method: A prospective cohort survey was conducted in 36 (aged 5.2-15.7yrs, mean age 11.1yrs, Male=58%) children with IBS who were evaluated at the National Police Hospital from December 2015 through December 2017. We collected dietary data of a low FODMAP diet using a food diary and underwent clinical data to assess compliance and delivered blood for analysis, monitoring of 13 micronutrient concentrations (retinol, thiamine, riboflavin, pyridoxine, folic acid, cyanocobalamin, ascorbic acid, 25-hydroxyvitamin D, α-tocopherol, zinc, selenium, prealbumin and ceruloplasmin).

Results: Overall, There were no significant differences in age, sex, IBS subtype, concomitant supplementary drugs and gastrointestinal symptom scores in this groups. Initial Laboratory tests revealed low serum concentration of retinol, thiamine, riboflavin, pyridoxine (4-pyrodoxic acid), folate, 25-hydroxyvitamin D and α-tocopherol in 24 IBS children, zinc in 6 children. One participant was low in zinc and one was low in selenium.

The benefit of low FODMAP diet in micronutrient status was equally apparent in all subtypes, but it shows significant different effects in micronutrient status according to the compliance. During the follow up duration, serum level of retinol, thiamine, riboflavin, 4-pyrodoxic acid, α-tocopherol and zinc was normalized in all subjects with high compliance subgroup (at least >75% the follow up duration, n.=15, 42%) compared with the lower compliance (n.=21, 58%, OR=19.2; 95% confidence interval 2.7-125.1; P =0.007). The mean time to resolution was 14.3 months (4.9-23.2) in the high compliance group.

Conclusion: In a prospective cohort study of patients with IBS, multiple micronutrient deficiency was very common and a diet low in FODMAPs effectively normalized the micronutrient status. It can support its use as a therapy for micronutrient deficiency in IBS children.
The role of ghrelin, obestatin and glutamate and their receptors in pathogenesis of the functional constipation in children

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Objectives and Study: Constipation is one of the most common gastroenterology diseases met by paediatricians. The role of enterohormones in pathogenesis of the functional constipation was not been unanimously described.

Ghrelin is the strangest agonist of the growth hormone secretagogue-receptor (GHSR). By its similarity to the motylin it also influences on motoric complex of the intestine. Activity of the obestatin is opposite to ghrelin - it reduces food intake, delays emptying of the stomach and spontaneous activity of isolated parts of the jejunum.

Glutamate is one of the main neurotransmitters in the central nervous system. Julio-Piper et al. revealed activity of this neurotransmitter in the intestines by confirmation of strong expression of the metabotropic receptor 7 for glutamate (GRM7) in the mucosae of mice. In further studies they revealed its' role in increasing water secretion into the lumen of intestine.

The aim of this study was to assign the role of ghrelin, obestatin and glutamate and their receptors in pathogenesis of the functional constipation in children.

Method: Study group consisted of 120 children aged 4-18 with functional constipation (diagnosed on the basis of Rome III criteria). Control group constituted 40 children in the same age without any disease of the gastrointestinal system.

During the gastroscopy and sigmoidoscopy biopsies for GHSR, obestatin receptor - GPR39 and GRM7 were taken. The concentration of those selected enterohormones was estimated by ELISA test. The Bioethics Committee of the Polish Mothers Memorial Hospital - Research Institute gave an agreement for this study - opinion from 23/SEP/2009 and opinion No 48/2017. Research carried out under the National Science Center No 2011/01/B/NZ7/0036

Results: There was a positive correlation between concentration of obestatin and colonic transient time (CTT) (p=LT; 0.05; rho=0.20). We have confirmed negative correlation between concentrations of obestatin and ghrelin (p=0.01; rho=-0.16). There was also positive correlation between expression of GPR39 in stomach and GRM7 in stomach (p=LT; 0.05; rho=0.40) like in GPR39 and GRM7 expressions in the large intestine (p=LT; 0.05; rho=0.47). Another positive correlation was discovered between expressions of the GHSR and GRM7 in the biopsies taken from the: stomach (p=0.02 rho=0.31) and large intestine (p=LT; 0.05; rho=0.23). Our study confirmed negative correlations between concentrations of ghrelin and obestatin in the serum (p=LT; 0.05; rho=-0.22) and between expressions of the GHSR and GPR39 both in stomach (p=LT; 0.05; rho=-0.45) and large intestine (p=LT; 0.05; rho=-0.29). There were no significant differences when groups were divided into sexes. Such correlations were not observed in the control group.

Conclusion: Our study revealed meaningful role of the ghrelin and obestatin in pathogenesis of the constipation. We proved that ghrelin increases CTT and obestatin decreases it. Not only those selected enterohormones themselves are important, but also their receptors. Another interesting finding is that we have proven that there is positive correlation between expression of the receptors for ghrelin and glutamate what can implicate that glutamate plays an important, anti-constipation role in pathogenesis of functional constipation in children.

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Therapeutic efficacy of probiotic Lactobacillus reuteri DSM 17938 and concomitant changes of gut microbiota in infants with functional chronic constipation

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Objectives and Study: Probiotics are commonly recommended for the alleviation of constipation symptoms. Recent studies have indicated that a probiotic Lactobacillus reuteri strain (DSM) 17938 alters composition of gut microbiota and exhibits therapeutic impacts on several infant diseases such as colic. However, there are a limited number of randomized clinical trials that evaluate the efficacy of probiotics in infants with functional chronic constipation. Based on these findings, we sought to evaluate the safety and the therapeutic efficacy of L. reuteri DSM 17938 along with magnesium oxide (MgO), a stool softener, in infants with functional chronic constipation.

Method: A double-blind, placebo-controlled, randomized study was conducted as follows. Sixty patients aged 6 months to 6 years old with a diagnosis of functional constipation according to the Rome IV criteria were recruited to this study and evaluated for their baseline condition of constipation by noting a defecation diary for 2 weeks. Subsequently, they were randomly assigned into 3 groups: group A received L. reuteri DSM 17938 alone (n=20); group B received both L. reuteri and MgO (n=19); group C received MgO alone (n=21). L. reuteri DSM 17938 was orally administered at the dose of 2x10⁸ colony-forming units (CFU) per day for 4 weeks. MgO was also administered orally at a dose of 30 mg/kg per day for 4 weeks. Clinical outcome was evaluated over time. In addition, changes in gut microbiota profiles were evaluated by high throughput sequencing of the V3-V4 region of the bacterial 16S ribosomal RNA gene.

Results: No adverse event was observed in this study. All three groups exhibited significant improvement in bowel movements (group A: \( p=0.0006437 \); group B: \( p=0.0095791 \); and group C: \( p=0.0050285 \)) compared with the baseline condition. Concomitant changes in gut microbiota were also observed.

Conclusion: Both L. reuteri DSM17938 and MgO were effective for bowel movements in infants with chronic constipation. The combination therapy of L. reuteri and MgO exhibited no additive/synergistic effect compared with the single treatments.

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Age-dependent reference values for the ‘Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R)’

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Objectives and Study: Symptoms associated with gastro-oesophageal reflux (GER) are often seen in children. However they are often aspecific, present in healthy infants and have a favourable natural course. Nevertheless, these symptoms form the cornerstone of gastro-oesophageal reflux disease (GERD) too. The I-GERQ-R is used to objectively score and evaluate reflux related symptoms, but has not been validated to diagnose GERD. Possibly this is due to the absence of age-specific reference values. The aim of this study was to determine age-specific reference values in healthy infants (0-28 months).

Methods: We performed a cross-sectional survey in healthy children aged 0-28 months during their regular check-ups at well-baby clinics. Caregivers completed the I-GERQ-R (total score 0-42). Spearman’s correlation coefficient (rs) was calculated to explore age-related trends.

Results: 411 infants (55.2% male) with a median age of 6.11 (IQR 1.0-22.6) months were included. Two infants (4 and 9 months old, I-GERQ-R score of 26 and 20) diagnosed with GERD by a healthcare professional were excluded. The maximum I-GERQ-R score was 27. The median I-GERQ-R score for all infants was 6.0 (P5-P95: 1.00-15.00). I-GERQ-R scores significantly decreased with age (rs = -0.582, p< 0.001, table 1). A similar decrease in regurgitation and colic associated symptom scores was seen (rs=-0.541 and rs=-0.398 respectively, table 1).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>0-2 m (n=77)</th>
<th>2-4 m (n=77)</th>
<th>4-6 m (n=45)</th>
<th>6-12 m (n=114)</th>
<th>12-18 m (n=58)</th>
<th>18-28 m (n=40)</th>
<th>TOTAL (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall I-GERQ-R score</td>
<td>10 (15-18)</td>
<td>9 (16-18.2)</td>
<td>6 (10.4-12)</td>
<td>5 (9-10.5)</td>
<td>3 (9-10.05)</td>
<td>2 (7.9-8.95)</td>
<td>6 (13-15)</td>
</tr>
<tr>
<td>median regurgitation score (p90-p95)</td>
<td>2 (6-6.10)</td>
<td>2 (6-8)</td>
<td>2.5 (5-5)</td>
<td>1 (3-4)</td>
<td>0 (1-3)</td>
<td>0 (2.9-5.9)</td>
<td>2 (5-6)</td>
</tr>
<tr>
<td>median colic score (p90-p95)</td>
<td>3 (8-9)</td>
<td>3 (6.2-8.1)</td>
<td>2 (4-5)</td>
<td>1 (5-6.25)</td>
<td>1 (4-5)</td>
<td>1 (3-3.95)</td>
<td>2 (5-7)</td>
</tr>
</tbody>
</table>

(Table 1- scores according to age group)

Conclusion: Gastro-oesophageal reflux symptoms measured by the I-GERQ-R, decrease in the first 28 months of life in healthy infants. We present the first age-dependent reference values for the I-GERQ-R.

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Comparison of tissue eosinophils of the gastrointestinal tract in children with functional abdominal pain disorders to normal references

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Objectives and Study: Although functional abdominal pain disorders (FAPDs) is very common in children and adolescents, its mechanism is not clearly evaluated yet. As micro-inflammation in the gastrointestinal (GI) tract including tissue eosinophilia was suggested as one of main pathogenesis of FAPD, this study aimed to evaluate tissue eosinophils in the entire GI tract of children with FAPDs compared to normal reference values.

Method: A total of 56 children and adolescents with FAPDs were recruited. All study subjects underwent esophagogastroduodenoscopy and colonoscopy with biopsies on the same day. Tissue eosinophil counts were assessed in 10 regions of the entire GI tract from the stomach to rectum. Tissue eosinophil counts of children with FAPDs were compared to those from normal references (n = 19 for upper GI tract, n = 41 for lower GI tract) in each 10 region.

Results: Eosinophil counts of the gastric antrum [4.1 ± 6.1/high power field (HPF) vs. 1.9 ± 1.3/HPF, \( p = 0.006 \)], the duodenum (13.0 ± 8.5 vs. 9.6 ± 5.3, \( p = 0.034 \)), terminal ileum (22.3 ± 17.6 vs. 12.4 ± 5.4, \( p = 0.009 \)), the cecum (23.0 ± 19.2 vs. 14.2 ± 6.1, \( p = 0.006 \)), the ascending colon (15.7 ± 9.5 vs. 12.0 ± 5.3, \( p = 0.013 \)), and the rectum (12.4 ± 6.1 vs. 3.3 ± 3.0, \( p < 0.001 \)) were significantly higher in children with FAPDs compared to those in normal controls. However, tissue eosinophils of the gastric body, transverse colon, descending colon, and sigmoid colon did not reveal any significant differences between children with FAPDs and normal controls.

Conclusion: Tissue eosinophil counts of the gastric antrum, small bowels, cecum, ascending colon, and rectum were significantly higher in children with FAPDs than normal controls. Therefore, eosinophils infiltration of the GI tract might be associated with the pathogenesis of FAPDs in children.

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Low FODMAP diet as a treatment modality for functional gastrointestinal disorders in children - preliminary results of a randomised cross-over control trial at a single tertiary paediatric centre in Singapore

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Objectives and Study: A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) effectively reduces symptoms in adult patients with functional gastrointestinal disorders (FGIDs) however its role in children is limited. Current data is based on low FODMAP Western diet which may not be applicable to Asian children due to inherent differences between Western and Asian diet. We investigated the effects of a low FODMAP diet (LFD) compared with a typical Singaporean diet (TSD) in children with FGIDs at a single, tertiary paediatric centre in Singapore.

Method: In a double blind, cross-over trial, children 7-17 years old with persistent abdominal pain who fulfilled the ROME III criteria for FGID completed a 7-day baseline period recording of gastrointestinal (GI) symptoms of abdominal pain, bloating, nausea, flatulence, and stooling pattern using a validated diary. Daily symptoms were rated using a 0-to 10-cm visual analogue scale. They were then randomised to either TSD or LFD (0.15 g/kg/day; up to 9 g/day FODMAP content) for 3 days, followed by a 5-day washout period, before crossing over to the other diet. The meals provided were designed by study dieticians who had undergone training for FODMAP diet. The diets were matched for total energy, protein and fat and fibre content. Daily GI symptoms were also recorded during both dietary interventions. Regular phone call follow up by the study team was done to ensure compliance and monitor intolerance. Patients were reviewed and symptom diaries were collected within 6 weeks following the second dietary intervention period.

Results: Of the eighteen enrolled children (median 12.5 years, range 8-17 years, 50% male, 83% Chinese ethnicity), 13 had commenced on either of the diets. Ten patients completed both dietary interventions while 3 did not complete the study for inability to tolerate or adhere to the prescribed diet. The rest of the enrolled subjects have yet to complete the study at the time of preliminary analysis. There were less bloating symptoms reported in the LFD compared to baseline (0.93 cm ± 0.3 versus 1.1 cm ± 0.4, p=0.05) and TSD (1.8 cm ± 0.76, p=0.19).

There was a trend towards lesser abdominal pain, less severe wind symptoms, less nausea reported in the LFD compared to baseline, however these results did not reach statistical significance. Abdominal pain severity was lesser in LFD compared to baseline (3.64 cm ± 1.01 versus 4.56 cm ± 1.1, p=0.21) and LFD compared to TSD (3.64 cm ± 1.01 versus 5.0 ± 1.3, p=0.25). Wind symptoms were less severe in LFD versus baseline (1.9 cm + 0.8 versus 3 ± 1.0, p=0.29) and TSD (3.6 cm ± 1.7, p=0.31). Similarly, nausea symptoms tended to occur less in the LFD compared to baseline (0.77 cm ± 0.41 versus 1.1 ± 0.69, p=0.29) and TSD (0.87 cm + 0.49, p=0.49). There was no difference observed in the stooling patterns between the two diets and when compared to baseline.

Conclusion: Our preliminary results suggest that children with FGID may benefit from a low FODMAP diet with a trend in improvement seen in the severity of abdominal pain, wind and nausea symptoms. It may be particularly effective in the subgroup of FGID patients with bloating as the predominant symptom.

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**GASTROENTEROLOGY - GI motility, GERD and functional GI disorders**

G-P-239

**Rome III abdominal pain-related functional gastrointestinal disorders and chronic gastrointestinal diseases among adolescents in Hungary**

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**Objectives and Study:** Abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) are common in childhood affecting 16.4% of children world-wide according to the Rome III criteria. The disorders are important due to their significant effect on quality of life, daily functioning, psychological co-morbidities and the notable health-care costs. Several studies have examined the prevalence of this condition from different countries, but epidemiological studies from Central-Eastern Europe including Hungary are scarce.

We conducted a national, cross-sectional, paper-based study in Hungary during April 2016 among 720 adolescents (age 11-18). The study sample was representative for school year, gender and region.

**Method:** Participants completed the Questionnaire for Paediatric Gastrointestinal Symptoms Rome III Edition (QPGS-III), questions regarding sociodemographic factors and chronic disease (celiac disease, lactose intolerance, inflammatory bowel disease, food allergy, other). We then selected a control group of 198 children (37.9%) reporting no pain (acute or chronic) in the last 3 months vs those living with AP-FGIDs. We used descriptive measures, Mann-Whitney U, \( \chi^2 \) test, Fisher's exact test to evaluate the prevalence of AP-FGIDs.

**Results:** 527 adolescents returned the questionnaire (a response rate of 73.19 %) and 522 (99.05%) (N=267, 51.1% girls, mean (SD) age 14.76 (2.4) years) were eligible for data analysis. 62 children reported at least one abdominal pain-related FGID (11.88%). We confirmed significant female predominance (\( \chi^2 \) test (df))=25.1 (1), p=0.000). Children attending schools in the capital reported significantly more AP-FGID (\( \chi^2 \) test(df) =4.8 (1), p=0.028) than in other regions, however living in a capital of a county was identified a protecting factor (Fisher's exact test, 0.049). The most prevalent AP-FGID was abdominal migraine (AM) (N=32, 6.1%), followed by irritable bowel syndrome (IBS) (N=24, 4.6%). 11 children (17.74%) from the AP-FGID group and 8 (4%) of the control group has reported chronic gastrointestinal disease (\( \chi^2 \) test (df)=13.7 (1), p=0.000).

**Conclusion:** In Hungary, the prevalence of AP-FGIDs is similar to other countries. We confirmed significant association of AP-FGIDs with female gender, which is in line with results from previous studies. However, we found significantly lower prevalence in children living in county capitals and higher in schools of the capital, which has not been reported before. The distribution of the type of AP-FGIDs was different from that in other countries, with the most frequent being abdominal migraine (AM). We found that adolescents with AP-FGIDs reported chronic gastrointestinal disease significantly more frequently. Our study raises need for longitudinal epidemiological studies and further research about the relationship between organic diseases and AP-FGIDs.

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GASTROENTEROLOGY - GI motility, GERD and functional GI disorders

G-P-240

Functional constipation in paediatric emergency department: a retrospective study. What we can do for these patients?

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Objectives and Study: Constipation is one of the most common complaints in children with a mean prevalence of 12%. Functional constipation (FC) accounts for more than 90% of childhood constipation and is currently diagnosed according to symptom-based Rome IV criteria. ESPGHAN/NASPGHAN Guidelines for FC, published in 2014, provides evidence-based recommendations for the evaluation and treatment. Therefore, the majority of constipated children, do not require any tertiary care assessment. However, previous data report an incidence of 0.4% of tertiary care Emergency Department (ED) visits for FC. Primary aim of this retrospective study was to depict incidence as well as the clinical features of children presenting to ED for FC. Secondary objective was to evaluate FC’s management in a third level hospital.

Method: We conduct a retrospective chart review of children presenting for FC at ED of Bambino Gesù Children Hospital from January 2016 to January 2017. A descriptive analysis on demographics and disease characteristics was performed.

Results: Overall, over 1 year 0.9% (409 out of 45000) of children presenting to the ED were diagnosed as having FC, of these 380 patients were included in the study (mean age 6.1 years [range: 1 month-18 years ]; M:F: 161/219). Presenting symptoms were: abdominal pain in 56% of patients, difficulty in passing stool in 40.2% (mean 7.2 ±12.9 days from last bowel movement) and rectal bleeding in 3.8% of patients. Percentage of assigned triage color code at ED admission were: 53% green, 41% white and 6% yellow. The mean ±SD wait time from entry to the first visit by physician was 147.9 ±119.3 minutes. A positive history of FC was present in 241 children (63.4%), 40.6% of them was on therapy with polyethylene glycol or lactulose. One hundred and fifty (39.4%) children underwent instrumental investigations or surgical evaluation: plain abdominal X-ray was performed in 13% of patients (51/380), abdominal ultrasound in 25% (94/380) and surgical examination in 4% (17/380). Overall 368 patients (96.8%) have been discharged while 11 children have been hospitalized for further evaluations.

Conclusion: The increased incidence of patients conducted for FC in a third level hospital suggests an overall poor familiarity to the international Guidelines for childhood FC among general pediatricians and low compliance by caregivers. Furthermore these data confirm that majority of FC related admission did not require acute management. In conclusion, the proper management of FC is crucial to reduce inappropriate ED admissions and long time permanence in the hospital. Network between different levels of assistance (primary, secondary and tertiary care) together with educational strategies for paediatrician and caregivers are needed to improve outcomes and quality of life of these patients.

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Adherence to polyethylene glycol treatment in children with functional constipation is associated with parental illness perceptions, satisfaction with treatment and perceived treatment convenience

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Objectives and Study: To assess treatment adherence in children with functional constipation (FC) and to evaluate the association with parental beliefs about medication, illness perceptions, treatment satisfaction and satisfaction with information about medication.

Method: Cross-sectional survey among parents of children with FC treated with polyethylene glycol. Adherence was measured using the Medication Adherence Report Scale (MARS-5, score 5-25), with higher scores indicating better adherence (scores ≥ 23 were defined as adherent). Beliefs about medication, illness perceptions, satisfaction with treatment and satisfaction with information about treatment were measured with the Beliefs about Medication Questionnaire, the Brief Illness Perception Questionnaire (B-IPQ), the Treatment Satisfaction Questionnaire for Medication (TSQM), and the Satisfaction with Information about Medication Questionnaire (SIMS). Associations between the questionnaire scores and adherence (MARS-5 score as a continuous variable) were analyzed with regression analyses. To test the effects of predictors on treatment adherence (MARS-5 score as a continuous variable), a hierarchical multivariate regression model with two blocks was created. The first block contained variables correlating both to MARS-5 according to Spearman's rank correlation (p< 0.20) in the current study and to adherence according to previous studies.

Results: 43/115 included children (37%) were adherent (MARS-5 ≥ 23). Spearman's rank correlation test revealed a statistically significant correlation between TSQM-convenience, TSQM-satisfaction, B-IPQ8 (emotions) and the MARS-5 score (rs 0.342, p=0.000; rs 0.258, p=0.006; rs -0.192, p=0.044). This suggests that parental perceived treatment convenience, satisfaction with treatment and illness perceptions may affect adherence in children with FC. The regression model contained the following predictors: BMQ-differential, B-IPQ4, B-IPQ8, TSQM-convenience, TSQM-satisfaction (block 1) and all 4 BMQ-subscales (block 2). In the hierarchical multivariate regression model, 22% of the variability of the MARS-5 score could be explained by the selected predictors. The TSQM-convenience score contributed the most to the model (β: 0.384, p=0.000).

Conclusion: Parents reported low adherence rates in their children with FC. Treatment inconvenience, dissatisfaction with treatment and the emotional impact of FC may negatively influence treatment adherence.

Disclosure of interest: Marc Benninga is a consultant for Shire, Sucampo, Astrazeneca, Norgine Coloplast, Danone, Frieslandcampina, Sensus and Novalac. The other authors have no conflicts of interest to declare.

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Long-term outcomes in children with refractory constipation treated by conservative therapy or by antegrade continence enema procedure (ACE)

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Objective: To compare outcomes in children with refractory constipation and overflow retentive stool incontinence (ORSI) under conservative therapy or by antegrade continence enema (ACE) procedure.

Methods: Follow-up data from 29 patients (median age: 94; min: 27, max. 142 months) with refractory constipation were recorded retrospectively. Refractory constipation was defined as ORSI persistence after 12 month-follow-up periods under conservative therapy (dietary fiber, oral osmotic laxatives, and rectal enemas). After this period, ACE was proposed as a therapeutic option. Eighteen patients have performed the procedure. Two outcomes were defined: 1. ORSI control; 2. Regular spontaneous evacuations, ACE or rectal enema were stopped.

Results: Three patients lost follow-up, two in the group ACE. Total follow-up period: conservative therapy: 31 months (20-72 m) and ACE: 29 months (12-74 m), p=0.184. The median period for ORSI control was achieved at 21 months in 3/11 in conservative group and at 1.2 months in ACE group, p=0.003. Successfully stopped using enemas at the end of follow-up: 3/10 conservative group and 8/16 ACE group, p=0.428. Surgical minor complications (leaking stoma and stenosis at stoma) occurred in 14/17 patients.

Conclusion: In refractory constipation, patients who underwent ACE procedure successfully stopped using their ACE more frequently and faster than children using rectal enemas.

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Prevalence of functional gastrointestinal disorders and socioeconomic and familial risk factors: a school-based survey in children and adolescents in Portugal

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Objectives and Study: Functional gastrointestinal disorders (FGIDs) are common in children of all ages and are emerging as an important cause of morbidity and high healthcare costs. Little is known about the prevalence of FGIDs in the pediatric population in Portugal. We aimed to assess the prevalence of FGIDs, and to search possible socioeconomic and familial risk factors for FGIDs, in Portuguese children and adolescents in a school setting.

Method: We conducted a school-based, prospective, multicenter study to collect data on 400 students aged 4-18 years (mean age 10.6 ±4.0 years) attending three semi-urban government schools in Paredes, a city located in the Northern region of Portugal. All children and adolescents were eligible for the study if consent was provided. The exclusion criteria were history of organic medical conditions or learning/language problems. Identification of FGIDs was based on answers to the Questionnaire on Pediatric Gastrointestinal Symptoms - Rome III Version (QPGS-RIII). The QPGS-RIII was translated from English into Portuguese according to standard procedures. The parent-report form was used for subjects between ages 4 and 9 years, and the self-report form was used for subjects between ages 10 and 18 years. A brief questionnaire about socioeconomic and familial factors was also delivered.

Results: The overall prevalence of FGIDs was 23.5% and was significantly higher in females than in males (29.4% vs 17.7%, p=0.006) and in adolescents than in children (28.6% vs 19.3%, p=0.03). Criteria for two or more diagnosis were met by 4.5% of the subjects and that superposition was significantly higher in females than in males (6.6% vs 2.5%, p=0.046). The most frequent disorders were functional constipation (12.5%), abdominal migraine (5.0%), irritable bowel syndrome (4.0%), childhood functional abdominal pain (2.8%) and aerophagia (1.8%). FGIDs were more common in subjects with employed mothers (75.5% vs 66.0%, p=0.006). Associations between the FGIDs and the remaining socioeconomic and familial factors were not statistically significant: living with both parents (96.8% vs 96.4%, p=1.00); only child (20.4% vs 21.3%, p=0.86); firstborn child (27.7 vs 20.9%, p=0.32); last-born child (38.3% vs 44.1%, p=0.32); mother’s education level (34.4% vs 40.6%, p=0.29); father’s education level (25.0% vs 33.6%, p=0.77); father’s occupational status (77.2% vs 83.2%, p=0.33); public water supply systems (79.1% vs 83.9%, p=0.29); public sewer systems (68.9% vs 78.0%, p=1.00); and domestic animals (71.3% vs 68.3%, p=0.59).

Conclusion: To our knowledge, this is the largest data available on FGIDs in the pediatric population in Portugal. This study is limited by the nature of the selected sample because results may not be representative throughout the country. Further studies are needed to evaluate the possible association between FGIDs and socioeconomic and familial factors.

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Supragastric belching: a behavioural disorder presenting in adolescents

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Objectives: Excessive belching is frequently reported in adult patients with gastro-oesophageal reflux disease and dyspepsia. Although postprandial gastric belching is considered a physiological mechanism for gastric venting, supra-gastric belching (SGB) is considered a distinct behavioural disorder with a prevalence of 3.4%. The aim of our study is to present paediatric cases of SGB syndrome diagnosed in our tertiary GI physiology unit.

Methods: Paediatric impedance-pH (MII-pH) studies performed at our Upper GI Physiology Unit from 2013 onwards were prospectively entered on an electronic database. Patients < 18 years, at the time the MII-pH study was performed, that were diagnosed with SGB syndrome were identified. The diagnosis of SGB syndrome was made if there were >13 episodes of SGB over 24 hrs and the patient reported belching as their main symptom. SGBs were identified by a rapid rise in impedance (≥ 1000 Ω) moving in an antegrade direction, followed by a return to baseline moving in the opposite direction.

Results: The total number of paediatric patients recorded was 325. Out of these, 2 patients were diagnosed with SGB syndrome (0.6%). The age of both children, at the time the MII-pH study was performed, was 15 yrs.

In case 1, the child presented to the emergency department and was later on referred to paediatric gastroenterology with intractable belching. On MII-pH there was normal acid exposure (0.5%) and normal number of reflux events (61). The child recorded 155 belching episodes corresponding to SGB. She made a full recovery following referral to paediatric psychotherapy team.

In case 2, the child presented to paediatric gastroenterology and reported significant belching and regurgitation. The MII-pH showed an increased acid exposure (15.1%) and pathological number of reflux events (141). The child recorded 950 episodes of belching which correspond to SGB. There was also co-existent ineffective oesophageal motility and rumination syndrome on manometry. The child showed partial symptomatic improvement with Baclofen and is awaiting behavioural therapy (see Image 1).

[Image 1: Belching episodes marked correspond to SGB.]

Conclusion: SGB syndrome is rare in paediatric patients and in our Unit presented only in adolescents. From our experience in adults, cognitive behavioural therapy can be used to treat this disorder and reduce both the number of SGBs and acid reflux related.

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Introduction: Persistence of dysphagia after treatment in patients with achalasia (surgical or balloon dilatation) is challenging and requires investigation for the presence of persistent mechanical obstruction at the oesophago-gastric junction (OGJ). Pre-treatment Integrated Relaxation Pressure (IRP) during HRM higher than 15 mmHg/cm suggests mechanical obstruction. The role of this cut-off value in post treatment persistent symptoms is controversial. A rapid drink test (200 ml water) and solid test meal (rice) have been proposed to help diagnosis of OGJ mechanical obstruction. We present 2 paediatric clinical cases where a rapid drink test and solid test meal during HRMI helped diagnosis and successfully guided further treatment.

Methods: Paediatric patients who were assessed following balloon dilatation for symptomatic achalasia with HRMI (Sandhill Scientific, CO, USA) were identified. A solid test meal was offered following the standard HRMI protocol of 10 liquid swallows (5mls each), a multiple rapid swallowing (MRS) and a rapid drink test (200mls) challenge.

Results: Two children with dysphagia following balloon dilatation for Achalasia type II were investigated with the above protocol.

A 15-year-old boy (case 1) presented with dysphagia (Dysphagia Composite Score: 6/45) and chest pain. He was diagnosed with Achalasia in 2011 and underwent 7 endoscopies for balloon dilatation since (latest in March 2016). The 10 liquid swallows revealed lack of normal peristaltic propagation, pan-oesophageal pressurisation in >20% of liquid swallows and the mean IRP was 6mmHg. MRS testing showed incomplete lower oesophageal sphincter inhibition and no after-MRS contraction. 200mls drink challenge showed liquid retention on impedance, pan-oesophageal pressurisation and an IRP of 19.4mmHg (measured at the last swallow). The solid test meal showed a gradual drop in impedance with bolus retention, pan-oesophageal pressurisation and an IRP of 19.6mmHg. His barium swallow showed barium retention with an 11cm column at 1 min and 6cm column at 5min.

A 13-year-old girl (case 2) presented with dysphagia (Dysphagia Composite Score: 12/45). She was diagnosed with Achalasia in 2015 and underwent 3 balloon dilatations since (latest in March 2016). The 10 liquid swallows revealed lack of normal peristaltic propagation, pan-oesophageal pressurisation and the mean IRP was 15mmHg. MRS testing showed incomplete lower oesophageal sphincter inhibition and no after-MRS contraction. 200mls drink challenge showed liquid retention on impedance, pan-oesophageal pressurisation and an IRP of 36.7mmHg. The solid test meal (Image 1) elicited chest pain and showed a gradual drop in impedance with bolus retention, pan-oesophageal pressurisation and an IRP of 23.4mmHg. Her barium swallow showed barium retention with a 21.1cm column at 1min and 20.8cm column at 5min.

Both children have been referred on for further surgical management.
Conclusion: Incorporation of a Rapid Drink Test and a Solid Meal Test during HRMI can confirm or reject the persistence of mechanical obstruction at the OGJ in patients with Achalasia with persistent symptoms after pneumatic balloon dilatation. This diagnosis has important clinical implications for further treatment i.e. new dilatation or Heller myotomy.

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Combined multichannel intraluminal impedance-pH monitoring in children with erosive esophagitis and nonerosive reflux disease

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Objective: To describe and compare the pH impedance findings of children with erosive and non-erosive esophagitis

Introduction: In children, gastroesophageal reflux is defined as involuntary returning of gastric content into the oesophagus. On the other hand, gastroesophageal reflux disease (GERD) occurs when the episodes of reflux are associated with nutritional, respiratory and oesophageal complications.

Oesophageal mucosal injuries are classified as erosive and non-erosive. Non-erosive esophagitis is present in 50-70% of patients with GERD, which is defined as the presence of reflux without injury of the oesophageal mucosa observed by endoscopy. Studies have found normal pressure of the inferior oesophageal sphincter, minor oesophageal motility alterations and minor acid exposition in patients with non-erosive esophagitis.

In recent years, Multichannel Intraluminal Impedance-pH (MII-pH) has emerged as an important diagnostic approach for GERD. It measures the quantity and characteristics of gastroesophageal reflux by describing the composition, pH, number of acid and non-acid episodes, time of contact, among others. It may also play a role in predicting oesophageal mucosal injury by employing different parameters such as the impedance baseline.

Methods: Endoscopy was performed in 26 patients who received care at the National Institute of Paediatrics during January 2016 and June 2017. They were classified based on endoscopic findings. Group A (Erosive esophagitis) 14 children and Group B (Non-erosive esophagitis) 12 children. Demographic data was evaluated and pH impedance measured the following parameters: number of reflux episodes; reflux index; standing oesophageal clearance time; supine oesophageal clearance time; longest episode of reflux measured in minutes; reflux episodes lasting more than 5 minutes; acid reflux; mild acid; non-acid episodes; and impedance baseline.

The U Mann-Whitney was used for the statistical analysis.

Results: There were no statistical differences between Group A and Group B in most of the pH-impedance parameters studied. However, no statistical differences were found in the time of total clearance and lower basal line of impedance in group A.

Conclusion: Despite the small simple size, we concluded the pH-impedance is not useful for establishing a diagnostic lesion of the oesophageal mucosa.
<table>
<thead>
<tr>
<th></th>
<th>Erosive Esophagitis</th>
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</table>

[PH-IMPEACE PARAMETERS]

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High resolution anorectal manometry in Colombian children, in a gastrointestinal physiology unit

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Objectives and Study: Anorectal manometry (ARM) is a useful test that allows evaluating the activity of contraction and relaxation of the anorectal sphincter. It provides information about the function of the anorectal sphincter (ARS), presence of reflexes, continence, defecation sensation and rectal compliance.

In recent years, high resolution ARM (HRARM) has replaced conventional manometry. There is a gap in the information on the reference values of HRARM in pediatric patients.

The main objective of the study was to describe the results found in HRARM performed on patients under 18 years of age between 2013-2016 at the San Ignacio University Hospital in Bogotá, Colombia.

Method: A descriptive cross-sectional study was carried out, all patients who met the inclusion criteria were included. All studies were performed with the same equipment: (ManoScan™ high-resolution manometry, Given imaging®).

A demographic description of clinical and measurable variables that were found in the population, using means, medians, standard deviations, 95% confidence intervals and ranges for quantitative variables was made. The STATA 12.1 program was used, using Pearson’s and Fisher’s X2 to establish the significance of qualitative variables and the Student’s t test for continuous variables.

Results: 48 patients were included. 56% (n = 27) were male. The average age at the time of performing the procedure was 10 years. The most frequent reason why the study was indicated was constipation in 81% of patients. Regarding to the values obtained, the average length of the ARS was 2.6 cm., The average pressure of the anal sphincter at rest was 54.7 mmHg. The volume of air inflated to the balloon required to trigger the rectoanal reflex was on average 34.9 cm3. Other variables such as maximum pressure in squeeze maneuver, percentage of relaxation in pushing maneuver and defecatory sensation were analyzed in patients who were not sedated for the procedure.

The variables were also described and analyzed by subgroups of age and sex. When comparing these results with the reference values of adult patients, important differences are found.

Conclusion: In pediatric population, it is necessary to improve the knowledge about HRARM. Studies of normal values in healthy population are needed, as well as studies of concordance with other tests.

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Objectives and Study: Achalasia is a rare esophageal motility disorder characterized by the failure of relaxation of the lower esophageal sphincter. The purpose of our study was to evaluate the manometric tracings of the children investigated for the suspicion of an esophageal motility disorder.

Methods: The study period was between October 2012 and November 2017. It is a retrospective study. In these 5 years, 16 conventional esophageal manometries were performed in our hospital. Patients had ages between 7 months and 17 years (age±SD=8±5.4 years). The parameters evaluated with the conventional esophageal manometry were the pressure of the lower esophageal sphincter, the relaxation of the lower esophageal sphincter after wet and dry swallows, the amplitude, speed and duration of the peristaltic waves of the esophageal body and the pressure of the upper esophageal sphincter. In 2 cases the results were not interpretable. Most of the patients were evaluated for dysphagia, one for thoracic pain, one for failure to thrive and two for feeding refusal.

Results: A total of 14 conventional esophageal manometry tracings were analyzed. In 4 cases achalasia was confirmed. The youngest patient diagnosed with achalasia was 4 years and 6 months old. Patients diagnosed with achalasia (age±SD=11±4,6 years, 3 boys) had values of the basal pressure of the esophageal sphincter of 39±17 mmHg. All the patients diagnosed with achalasia had incomplete relaxations of the lower esophageal sphincter after wet swallowing. Two of the patients with achalasia had low parameters of the motility in the esophageal body, and one patient had high values of the amplitude of the peristaltic waves of the esophageal body. Two patients diagnosed with scleroderma (6 and 14 years old, 2 girls) were evaluated for dysphagia, but no changes in the esophageal manometric parameters were found. One patient, previously diagnosed with neurofibromatosis, was evaluated for feeding refusal, had high values of the pressure of the lower esophageal sphincter (60 mmHg), but with normal relaxation after wet swallowing. Six patients, with no chronic diseases diagnosed at the moment of the investigation had normal esophageal manometry parameters.

Conclusion: Esophageal motility disorders are a rare finding in paediatric patients. Achalasia was the most frequent esophageal motility disorder diagnosed by conventional esophageal manometry in our hospital.
Neuropathic gastrointestinal pain in children with RASopathies: a single center experience

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Background and Aim: Pain in RASopathies is an underreported clinical problem highly affecting the quality of life in children. Anecdotal reports about individuals with RASopathies experiencing neuropathic pain have been published. Pain is often reported as of gastrointestinal (GI) origin. Objective evaluation of neuropathic GI pain and possible treatment program are still lacking. Aim of our study was to assess prevalence of GI pain in a group of individuals affected by RASopathies and GI disorders.

Methods: Between April 2016 and June 2017, 80 patients with molecular diagnosis of Noonan syndrome (NS), Costello syndrome (CS) and cardiofaciocutaneous syndrome (CFCS) were prospectively enrolled at a single center. Past medical history of each patient was reviewed. According to patients' IQ and adaptive behavior profiles, we administered different standardized questionnaires. Questionnaires were filled in by patients if able (normal IQ evaluation) or by parents/clinicians. Specifically, we used: WONG-BAKER scale, Visual analogue scale (VAS), r-Face-Legs-Activity-Cry and Consolability (r-FLACC) scale, Neuropathic Pain Symptom Inventory (NPSI), Non Communicating Children's Pain Checklist-Revised (NCCPC-R) in non-communicating children, Brief Pain Inventory (BPI), Rome III questionnaire, to screen for functional gastrointestinal disorders.

Results: The study included 42 subjects with NS, 17 with CS and 21 with CFCS (30 males, mean age 9.3 ± 8.3 years). Aerophagia and constipation were the most frequent detected GI disorders. The overall prevalence of chronic GI pain was 55% in the cohort. Chronic GI pain was significantly associated with the diagnosis of functional abdominal pain (p=0.001) aerophagia (p=0.042), irritable bowel syndrome (p=0.047), functional constipation (p=0.05), adolescent rumination syndrome (p=0.006), as assessed by Rome III criteria. No statistically significant differences were observed when considering all other functional GI disorders.

Conclusions: Chronic GI pain represents a high prevalence clinical problem in patients with RASopathies. RASopathies are caused by germline gain of function mutations in genes belonging to the RAS/MAPK pathway, therefore perception of pain in patients with RASopathies can be the result of an altered modulation and elaboration of the painful stimulus. Further and multicenter studies should be performed to characterize GI disease and pain in these children to improve their quality of life.
Hair cortisol measure in Hirschsprung patients as an indicator of stress; a prospective case-control study

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Objectives and Study: Although surgery is considered curative in children with Hirschsprung disease (HSCR), patients are at risk to suffer from intestinal dysfunction. Fecal incontinence appears to be a major stress factor for affected persons and might have a significant negative impact on quality of life. Measure of hair cortisol has become an important and valid method to detect stress levels. In contrast to salivary or serum cortisol, hair cortisol remains stable over time and serves therefore as a retrospective stress-journal.

We aimed to evaluate the stress level in HSCR patients compared to healthy controls (HC) by measuring the hair cortisol concentration and comparing it with type of HSCR and long-term outcomes.

Method: Prospective case-control study of 66 HSCR patients and 117 HC older than 6 years between July 2015 and December 2017. Patients demographics and characteristics were obtained from medical charts. Questionnaires about digestive symptoms (QGPS, ROME III criteria) and stress (Dubow) were obtained.

Hair sample (length 3 cm representing the previous 3-month period) was obtained from the posterior vertex of the skull, as close as possible to the scalp. After extraction of hair cortisol following a strict protocol, cortisol measure was performed by using a saliva enzyme-linked immunosorbent assay (EIA) kit from ALPCO® with a sensitivity of 1.0ng/ml. A quality-control hair sample and internal controls were used in every extraction to ensure the validity of the extraction and the intra- and inter-assay variation. Descriptive data are presented as median [interquartile] for continuous variables and as frequency (%) for categorical variables. Statistical analysis was performed by using Wilcoxon log rank sum test and chi square test for continuous and categoric variables respectively. Non-symmetrically distributed data was logarithmically transformed. Pearson and Spearman correlation tests were performed.

Results: Final analysis was performed in 39 HSCR patients (23 males; 58%) and 79 HC (41 males; 53%), with hair sample available. Median age at study inclusion was 12.4[8.3, 18.3] and 12.9[10.2,15.2] years in HSCR and HC respectively (p>0.05).

Hair cortisol concentration was 59.6 pg/mg hair [25,128.6] in HSCR and 47.6 [15.3,91.1] in HC respectively (p=0.5). A correlation was seen between age at hair collection and hair cortisol concentration (r=0.29, p=0.002) in HSCR and HC with significant higher cortisol levels in subjects aged 12 years and older (p=0.004).

Questionnaires about stressful events were obtained from 35 patients and 70 HC. A total number of 55 and 106 stressful events were detected in HSCR and HC, respectively (p>0.05). No correlation between stressful events and hair cortisol level was found (p>0.05).

No association between type of HSCR (short vs longer/total colonic forms) and hair cortisol concentration was found (p>0.05). A trend toward an association of fecal soiling with higher hair cortisol level was seen (p=0.07).

Conclusion: Hair cortisol concentration was comparable in HSCR and HC. No correlation was found between stressful events, type of HSCR and hair cortisol level. There is a trend toward an association between fecal incontinence and higher hair cortisol content. Studies on QoL are ongoing.

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PPM1D deficiency is a possible cause for chronic constipation in patients with intellectual disability syndromes

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Objectives and Study: De novo truncating germline mutations in the last and penultimate exons of PPM1D have recently been shown to cause intellectual disability (ID) syndromes with behavioral problems, hypotonia, broad-based gait, periods of fever and vomiting, high pain threshold, short stature, small hands and feet and facial dysmorphic features. Although described in more than every second patient, constipation has so far not been recognized as an additional feature of the syndrome.

Case outline: A 6-year-old boy with etiologically unexplained ID syndrome presented at the pediatric gastroenterology outpatient clinic due to chronic constipation. Pregnancy, birth and postnatal adaptation were normal. The boy showed an unremarkable development until the age of 1 year, where the parents noticed motoric delays. He started to walk at the age of 3 years and until now he verbally expresses himself with vocals only. Ophthalmologic investigations showed strabismus and hyperopia. The constipation was first diagnosed at the age of two years and treated with macrogol. This led to regular soft stools with overflow diarrhea, incontinence, and the need for diapers during day and night. Abdominal pain, vomiting or abnormalities upon examination of the abdomen were not present. Laboratory tests showed no hypothyroidism, celiac disease, signs of malnutrition or inflammation and normal values in full blood count and liver and kidney function. Further investigations revealed unremarkable results in metabolic screening, molecular karyotype, molecular testing for fragile-X-syndrome, methylation-analysis in 15.q11-q13 and fibroblast cultures from skin biopsy. Ear-nose-throat- investigation and hearing examination indicated normal status. Cranial MR imaging showed a discrete enlargement of the outer cerebrospinal fluid spaces without progression compared to preliminary assessment or further abnormalities. For further evaluation whole-exome-sequencing (WES) was performed.

Results: WES revealed a de-novo stop-mutation in the penultimate exon of the PPM1D gene. The clinical presentation with severe chronic constipation in our patient is in line with the so far only one clinical study by Jansen et al. (Am J Hum Genet. 2017) where 8/13 (55%) of the patients were described with constipation.

Conclusion: PPM1D deficiency needs to be considered as a causal mechanism in patients with ID syndrome and chronic constipation. Further studies are required to better understand the importance of the Mg2+/Mn2+-dependent protein phosphatase 1D, which is known to be involved in the DNA damage response, for the proper function of the gastrointestinal system.

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Salivary pepsin measurement cannot be used for the diagnosis of infant gastro-oesophageal reflux disease

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4VU University Medical Center, Amsterdam, Netherlands

Objectives and Study: An adequate and reliable tool for the diagnosis of gastro-oesophageal reflux disease (GORD) in infants is currently lacking. Salivary pepsin has been proposed as a highly specific, non-invasive diagnostic marker for GORD in adults, with a cut-off for test-positivity of > 210ng/ml using the Peptest® device. Little is known about its diagnostic value for GORD in infants. Therefore, we used the Peptest® device in an aim to establish normative values of salivary pepsin in healthy infants.

Method: Parents of healthy infants (age 0 - 18 months) attending well-baby clinics in the Netherlands for their regular check-ups were invited to participate. GORD symptoms were assessed by the Infant Gastroesophageal Reflux Questionnaire Revised (IGERQ-R) and infants with a score ≤ 16 were considered eligible. Parents were instructed to collect their infants' saliva over 2 consecutive days one hour after each feeding (maximum 5 samples per day). All saliva samples were analysed using Peptest® within 7 days after collection according to the manufacturer's instructions. The established adult cut-off for GORD of > 210ng/ml was used to indicate Peptest® positivity (accurate range of detection 0 - 500ng/ml).

Results: Of 164 infants that were approached, 159 were eligible to participate based on their IGERQ-R scores. Saliva samples were successfully collected and returned for 63 infants (29 female, median age 7.4 months (range 3.0 - 9.9), comprising a total of 274 samples (median 4 samples per infant, range 1 - 7 samples). Healthy infants had a median pepsin concentration of 433ng/ml (IQR 108 - 500), with 58/63 (92%) infants having at least one value > 210 ng/ml, and 42 (67%) having at least one value > 500ng/ml.

[Figure 1]
Minimum, mean and maximum pepsin concentrations in 63 healthy infants over two-day collection. Values > 500 ng/ml were revised to a figure of 500ng/ml and marked as inaccurate. Red dotted line is the previously established cut-off value of 210ng/ml for GORD in adults.

**Conclusion:** Almost half of the samples of healthy infants were above the accurate range of detection of Peptest®, hampering the establishment of normative infant ranges. Our results suggest that salivary pepsin measurement by Peptest®, at least in its current form, cannot be recommended for the clinical management of GORD in infants.

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Use of magnesium-containing mineral waters for treatment of functional constipation among children and teenagers

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Method: Study of patients included medical examination, analysis of results of laboratory, ultrasonic, and instrumental gastrointestinal examination methods, and filling in special questionnaires. The study covered 95 children who had the 'functional constipation' diagnosis (Rome IV - Functional GI Disorders: H3a. 'Functional Constipation'). Using the simple randomization method, the children were arranged in two groups. The basic group included 55 children who received basic treatment (the sparing/training regime, nutritional therapy, exercise therapy, and revitalizing massage) and internal administration of magnesium-containing water "Donat Mg" with individual calculation of single doses (3 μL/kg). The comparative group (40 children) was receiving basic treatment only. The examined patient groups were comparable in terms of nature of disorder, sex, and age. Duration of the treatment was 18 days. To evaluate the results, parametrical methods of statistical processing were used. Qualitative values were compared using the χ² method. The reliability of difference in values was deemed verified at significance level of p< 0.05.

Results: In the basic group, the effect of regular everyday stool was noted on Day Five of the protracted treatment among 45.5% of patients, and on Day Nine, among 65.5% of patients. By the end of the protracted treatment, regularity of stool was noted among 91% of children. In the comparative group, positive dynamics was much less marked, and constituted, respectively, 20% (on Day 5), 30% (on Day 10), 47.5 % (on Day 18) (p < 0.05). Assessment of the nature of stool using the Bristol scale showed that before the treatment stool in both groups had corresponded to Type 1 or 2. Nature of the stool among patients in the basic group at the background of mineral water administration began to change; by Day 5 of the observation, it corresponded to Type 2 or 3 (among 51.0% of patients), and to Type 3 or 4 on Day 10 (among 67% of patients). On Day 18, 89.1% of patients had soft formed stool; there were no complaints at all in respect of defecation difficulties or pain. In the comparative group, changes in the nature of stool began to show (among 35% of patients) as late as on Day 10 of the observation, and corresponded to Type 2 or 3 (p < 0.05). Our technique of formation of a reflex for morning defecation using mineral water demonstrated its efficiency. The reflex was observed beginning from Day 5 or 6 of use of the technique, and its stability continued throughout the entire observation period (Figure 1).
Conclusion: Use of magnesium-containing mineral waters is an efficient method to correct functional constipations among children. Simplicity and affordability of the method and absence of adverse effects make magnesium-containing mineral water the remedy of choice for the treatment of functional constipations among children.

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Prevalence of functional gastrointestinal disorders in young European children

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Objectives and Study: Paediatric functional gastrointestinal disorders (FGIDs) are a common problem worldwide. So far, epidemiologic data about FGIDs with respect to infants and younger children in Europe are limited.

Method: Children were enrolled if they were (1) aged 0 - 48 months, (2) attending a general paediatrician (Belgium, Italy) or a well-baby clinic (The Netherlands) for a regular check-up. Separate study questionnaires were developed for infants aged 0 - 6 months and for children aged 7 - 48 months. Questionnaires evaluated the clinical history, symptoms, socio-demographic information on the family and exposure to stressful life events. FGIDs were defined according to Rome IV criteria. After informed consent, questionnaires were completed at the site of inclusion.

Results: In total 2751 children were included: 1229 infants aged 0 - 6 months and 1522 children aged 7 - 48 months. The prevalence of FGIDs in infants aged 0 - 6 months and 7 - 48 months was 18.9% and 9.5%, respectively. The most common disorders were colic (8.7%) and dyschezia (4.1%) in infants and functional constipation (6.2%) in toddlers. Prevalence data regarding all FGIDs are summarised in the Table. Univariate regression analyses demonstrated that age was associated with having any FGID among infants aged 0 - 6 months (p < 0.01), rural living environment (p 0.04) and having an income not meeting essential needs (p 0.04) were associated with having any FGID in children aged 7 - 48 months. However, multivariate regression analyses showed no statistically significant association.

Conclusion: FGIDs are common in a community sample of young children in Belgium, Italy and The Netherlands. Prevalence tends to be higher in the first months of life. Colic and dyschezia are most prevalent among infants and functional constipation is most common among toddlers. Risk factors for having an FGID were age (among infants) and rural living environment and an income not meeting essential needs among toddlers.

<table>
<thead>
<tr>
<th>FGID</th>
<th>0 - 6 months (n = 1229)</th>
<th>7 - 48 months (n = 1522)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant regurgitation</td>
<td>48 (3.9%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Rumination syndrome</td>
<td>32 (2.6%)</td>
<td>14 (0.9%)</td>
</tr>
<tr>
<td>Cyclic vomiting syndrome</td>
<td>8 (0.7%)</td>
<td>19 (1.2%)</td>
</tr>
<tr>
<td>Infant colic</td>
<td>107 (8.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Functional diarrhoea</td>
<td>N/A</td>
<td>14 (0.9%)</td>
</tr>
<tr>
<td>Infant dyschezia</td>
<td>51 (4.1%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Functional constipation</td>
<td>18 (1.5%)</td>
<td>94 (6.2%)</td>
</tr>
<tr>
<td>Any FGID</td>
<td>232 (18.9%)</td>
<td>144 (9.5%)</td>
</tr>
<tr>
<td>Multiple FGIDs</td>
<td>31 (2.5%)</td>
<td>4 (0.3%)</td>
</tr>
</tbody>
</table>

[Prevalence of all FGIDs per age group]

FGID: gastrointestinal disorder; N/A: not applicable

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Acoustic signal of silent tracheal aspiration in children with oropharyngeal dysphagia

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Objective: The aim of this study was to characterize the acoustic signal of silent tracheal aspiration in children with oropharyngeal dysphagia (OPD).

Methods: Thirty-two children with OPD were examined with combined digital cervical auscultation (DCA) and videofluoroscopic swallow study (VFSS). Power spectral density (PSD, in $1/\sqrt{Hz}$) of the acoustic signal from a sequential series of five liquid swallows was used for comparisons between children who silently aspirated and children who did not aspirate at VFSS.

Results: Among 32 children, 14 were excluded due to either DCA/VFSS artifacts or non-silent aspiration (cough, choking). The remaining 18 participants (median age 6 years range 2-12.8) were classified based on VFSS as aspirators ($n=8$) and non-aspirators ($n=10$). The PSD curve of aspirators presented an ascending pattern (1st vs. 5th deglutition: 695.2 vs 4421.9 $1/\sqrt{Hz}$), while the curve of non-aspirators was flat (1st vs. 5th deglutition: 509 vs 463.4 $1/\sqrt{Hz}$), with marked differences being observed from the 3rd measure onwards ($P < 0.001$).

Conclusion: In this study, digital cervical auscultation was able to characterize silent tracheal aspiration in children with oropharyngeal dysphagia. This non-invasive technique demonstrated aspiration by an increase in the power spectral density curve in aspiration sounds.

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Sleep disturbances in adolescents with gastroesophageal reflux disease: the school-based study

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Objectives and Study: Many clinical studies have demonstrated a relationship between gastroesophageal reflux disease (GERD) and sleep disturbances in adult patients. Data about this relation in children and adolescents are limited, especially in studies based on the school samples.

Method: 465 urban Siberian (Krasnoyarsk) adolescents aged 12-18 were asked for belching and/or heartburn presence in the past month and screened with Russian version of Gastroesophageal Reflux Disease Questionnaire (GerdQ). The sum of the scores for the six GerdQ questions ranged from 0 to 18 and was defined as the GerdQ score, with a score ≥ 8 indicative of high probability for GERD. Additionally adolescents were tested for sleep quality with Pittsburgh Sleep Quality Index (PSQI), 9 questions from section #5. Questions and answers variants have shown in table 1. Answers were pointed from “0” (“not during the past month”) to “3” (“three or more times a week”). “Sleep disturbance score” was calculated as the sum of points for all 9 questions. Data are shown as median (25-75% quartiles). Kruskal-Wallis test was used.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cannot go to sleep within 30 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Wake up in the middle of the night or early morning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Have to get up to use the bathroom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Cannot breathe comfortably</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Cough or snore loudly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Feel too cold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Feel too hot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Have bad dreams</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: Progressive positive associations were detected between “Sleep disturbance score” and selected adolescents groups with an increase in the level of upper GI motility disturbance: no belching and/or heartburn presence group (n=330) - 4.87 (4.66-5.09), belching and/or heartburn complaints but no GERD group (n=110) - 6.24 (5.88-6.59) and GERD high probability group (n=25) - 7.95 (6.89-9.02), Kruskal-Wallis test p< 0.001).

Conclusion: In this school-based sample of urban adolescents we observed a strong association between GERD and sleep disturbances, that may reflect the effect of nighttime symptoms on sleep quality. On the other hand, sleep disorders may be caused by anxiety and depression associated with GERD.
Objectives and Study: Functional gastrointestinal diseases (FGIDs) consist of a variety of chronic or recurrent symptom-based disorders not explained by known structural or biochemical abnormalities. FGIDs are multifactorial conditions with different pathophysiologic mechanisms including altered motility, visceral hyperalgesia, genetic, environmental and psychological factors. Anxiety and depression often co-occur in patients suffering from FGIDs, contributing to the multidimensional status of these conditions. According to Rome IV classification, the pathophysiology can be associated with dysfunction at different level of the Gut-Brain Axis, the bidirectional pathways between the gastrointestinal tract and the central nervous system. Several studies suggest that the increased psychological tendency to report pain can be driven by hypervigilance and underlies the decreased pain threshold in patients suffering from functional gastrointestinal diseases. The aim of our study was to explore Gut Brain Axis in children affected from FGIDs to establish if the axis alteration can affect also visual attentional processing in these patients.

Method: 30 patients aged between 7 and 15 years old recruited at a pediatric gastroenterology clinic were enrolled. Of these patients: 11 were affected by a functional gastrointestinal disorder (ie, functional constipation or functional abdominal pain) and 19 patients were affected by an organic disease (ie, celiac disease or gastro-esophageal reflux). The two groups, matched for age and general cognitive performance, performed an oculomotor capture task in which a highly salient target had to be foveated in each trial. In 60% of cases the target was accompanied by the onset of an additional task-irrelevant distractor.

Results: In the condition “presence of a distractor” both groups suffered a cost in performance with a higher mean value of saccadic movements compared with the condition of absence of a distractor (p< 0.001). However, the group of patients with FGIDs showed remarkably delayed saccadic latencies in distractor present conditions compared to the condition “absence of distractor” (p< 0.001), probably due to the need to solve target-distractor competition (Figure 1).
Conclusion: Patients affected by FGIDs show a general difficulty in selecting relevant versus irrelevant sensory stimulation, probably as an expression of the hypervigilance state. This general difficulty might critically underlie the effort in the correct discrimination of other types of sensory inputs. This on one hand can erroneously increase the magnitude of ordinary stimuli enhancing their perceived intensity, and on the other allow the development of more complex forms of attentional dysfunctions such as stimulus-specific attentional biases. This study can help to explore the alteration of the Gut-Brain Axis in patients affected by FGIDs with a non-invasive method and open the way for further studies.

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A decrease in hydrogen production in distal ileum and colon is associated with improvement of symptoms in children with functional abdominal pain

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Objectives and Study: Functional abdominal pain (FAP) has a high prevalence among adolescents and school-age children. In Mexico the prevalence of IBS in children is 6.4%. Small Intestine Bacterial Overgrowth (SIBO) is a potential cause of IBS. SIBO is diagnosed by hydrogen breath test (HBT) with either glucose or lactulose. At our hospital HBT is performed with lactulose. There is a group of patients who do not meet the current criteria for SIBO as hydrogen begins to rise after 90 minutes. After 90 minutes the oro-cecal transit is completed, thereafter any rise of hydrogen is being produced in colon. If the current SIBO criteria is used this group of patients would have a negative study. We hypothesise that this group of patients have an increased hydrogen production in the colon that may be caused by colonic bacterial overgrowth or colonic dysbiosis (mainly anaerobic bacteria). Based on the latter hypothesis we treated these patients with secnidazole and a diet low in lactose, sorbitol and legumes (modified FODMAP diet). The aim of this study was compare the HBT before and after the treatment and compare the symptoms improvement

Method: Prospective, analytic, comparative study of 14 children with FAP (Rome IV criteria) who underwent a baseline Lactulose HBT that showed a rise of hydrogen after 80-90 minutes. Gastrolyzer® device was used. Lactulose was given at a dose of 0.5 g/kg (maximum 10 g), and measurements were taken every 20 minutes during 180 minutes. We complied with the latest North American Consensus recommendations for the HBT. All patients were treated with secnidazole 30/mg/kg/day (2 cycles of 3 days each, 1-week rest in between), and modified FODMAP diet. 6 weeks later second LHBT was performed, and improvement of symptoms was classified as Total: None pain; Partial: Still have pain but less days or less intense; None: Without pain. Statistical analysis was done using SPSS software 20.0. Differences among times were assessed by paired-samples t test. Area under the curve (AUC) responses were calculated by trapezoidal rule. Results were expressed as mean and standard error of the mean (SEM). A p-value of < 0.05 was considered to be statistically significant.

Results: Of the 14 patients, 8 were boys (57%). Mean age was 6 years (± 1.5). We found significant differences after minute-80 between the first and second LHBT (figure 1A). Figure 1B shows the differences in the AUC of each patient. 13 (92%) of then showed total symptom improvement and 1 partial improvement.
**Conclusion:** SIBO is a potential cause of functional gastrointestinal disorders in paediatric patients, however, there is a subgroup of patients who may have colonic dysbiosis or bacterial overgrowth in the colon, and who improve with antimicrobial therapy directed to anaerobic bacteria and a low FODMAP diet. Randomized controlled trials need to be conducted in order to test this hypothesis.

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Lactose and lactulose hydrogen breath test in children with functional abdominal pain

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¹Instituto Nacional de Pediatría, Mexico, Mexico

Objectives and Study: Functional abdominal pain (FAP) is common in children and adolescents. The etiology of functional abdominal pain in children is multifactorial, however SIBO and lactose intolerance can be the cause of this symptomatology. Lactose malabsorption is defined in the hydrogen breath test (HBT) with lactose an a rise of more than 20 ppm after 90 minutes, while SIBO is defined in the HBT with lactulose as the elevation of 20 ppm before 90 minutes. The objective of this study was to compare the HBT with lactose and lactulose in children with FAP.

Methods: Prospective, analytical, comparative and observational study in 32 children with functional abdominal pain according to the Rome IV criteria; Gastrolyzer was used for HBT test and were performed according to the recommendations of the North American HBT consensus. HBT with lactose: Lactose was given 0.5 grams per kg maximum 25 grams. A positive elevation of more than 20 ppm after the 90th minute was considered positive. HBT with lactulose: lactulose was given 0.5 grams maximum 10 grams. It was considered positive elevation more than 20 ppm before 90 minutes. The statistical analysis was performed using SPSS software 20.0 (SPSS, Chicago, IL). Differences among times and groups were assessed by paired-samples t test or Wilcoxon. Area under the curve (AUC) responses were calculated employing the trapezoidal rule. Results were expressed as mean and standard error of the mean (SEM) or median (minimum and maximum). A p-value of < 0.05 was considered to be statistically significant.

Results: The mean age of children was 7.2 years. 17 (53%) were males. Of the 32 patients (50% had a positive HBT), 31.3% had a positive lactose breath test (lactose malabsorption) and 28.2 % had a positive lactulose breath test (SIBO), comparing proportions with Fisher test it has a p>0.05. However comparing the AUC of the patients positive with lactose vs negative with it we found statistically significant differences (p< 0. 05) the same occurs in the patients positive with lactulose and negative with it (Figure 1A and IB).
**Conclusion:** In children with functional abdominal pain it is important to perform a HBT to rule out lactose malabsorption or SIBO, due 50% of our population has positive lactulose or lactose HBT.

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Initial diagnosis of functional gastrointestinal disorders in children increases a chance for resolution of symptoms

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Objectives and Study: Based on currently available Rome IV criteria diagnosis of functional gastrointestinal disorders (FGID) should be positive, and not based on the exclusion of organic disease. However, the studies evaluating whether early recognition of FGID has an impact on resolution of symptoms is not determined yet.

Therefore, aim of this study was to describe FGID presented in tertiary medical center, characteristics of the patients and results of the diagnostic work-up together with the outcome during the follow up.

Method: This was a retrospective, single center, observational study. Data from all patients who were referred to the tertiary medical center with symptoms suggestive FGID and who were subsequently diagnosed with FGID based on Rome III criteria from January to December 2015. Data was extracted from the hospital electronic and chart information system. Each chart was methodologically reviewed for data including gender, age at diagnosis, diagnosis, physical exam and anthropometrics, treatment, follow up and symptom control at the end of follow up. The primary objective was to present characteristics of children with FGID. Secondary objectives were to compare diagnostic and treatment strategies, to give prognostic factors for symptoms improvement in children with FGID.

Results: During study period 294 children (mean age 8.9 years, range 1-18 years; 129 male and 165 female) with final diagnosis of FGID were treated in our center and who had at least one follow-up visit. Majority had functional constipation (104, 35.4%), followed by functional abdominal pain (90, 30.6%), irritable bowel syndrome (50, 17%), functional dyspepsia (37, 12.6%), functional nausea (10, 3.4%) and abdominal migraine (3, 1%). Differences between mean age at diagnosis, anthropometric parameters, presence of alarm symptoms are presented in the Table.

Regression model found that only significant factor associated with improvement of symptoms is the establishment of functional diagnosis at the first visit (hazard ratio 2.163, 95% CI 1.029- 4.544); other parameters included in the model sex, age and disease type were not significantly associated with symptoms resolution. There was no association between improvement of symptoms and presence of alarm signs/symptoms (weight loss, nocturnal symptoms and severe vomiting) at diagnosis. Furthermore, in pain symptoms (FAP, IBS and dyspepsia) no treatment positively correlated with pain improvement.

<table>
<thead>
<tr>
<th></th>
<th>Constipation (n=104)</th>
<th>Functional Abdominal Pain (n=90)</th>
<th>IBS (n=50)</th>
<th>Dyspepsia (n=37)</th>
<th>Migraine (n=3)</th>
<th>Functional Nausea (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>4.9 (1-16.3)</td>
<td>9.6 (1.9 to 16.5)</td>
<td>12.9 (5-18)</td>
<td>12.9 (5.6 to 17.7)</td>
<td>10 (6.9 to 12.9)</td>
<td>8.3 (4 to 17.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wright for Age Z score</td>
<td>0.56 (-3 to 3.54)</td>
<td>0.8 (-1.2 to 2.66)</td>
<td>0.42 (-2.3 to 2.66)</td>
<td>0.49 (-1.88 to 2.64)</td>
<td>0.51 (-1.56 to 1.94)</td>
<td>1 (-0.1 to 2.43)</td>
<td>0.432</td>
</tr>
<tr>
<td>Height for Age Z score</td>
<td>1.12 (-2.1 to 3.8)</td>
<td>1.37 (-1.1 to 3.5)</td>
<td>0.84 (-1.3 to 3.1)</td>
<td>0.87 (-1.8 to 3)</td>
<td>1 (-0.8 to 2.5)</td>
<td>1.8 (0-3)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Alarm symptoms present (n,%)</td>
<td>8 (7.7%)</td>
<td>32 (35.6%)</td>
<td>25 (50%)</td>
<td>17 (45.9%)</td>
<td>3 (100%)</td>
<td>6 (60%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

[Table 1]
**Conclusion:** Regardless of initial diagnosis of functional gastrointestinal disorders positive diagnosis at the first visit increases a chance for resolution of symptoms.

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Intestinal pseudoobstruction: Another phenotypic spectrum of CDG-1m?

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²Koç University, Istanbul, Turkey

Objective: Congenital disorders of glycosylation (CDGs) are a group of metabolic diseases caused by mutations in genes resulting abnormal protein and lipid glycosylation. Dolichol kinase (DOLK) catalyzes the last step in biosynthesis of dolichol phosphate which is needed for protein N-glycolysation. Biallelic mutations in the gene for DOLK result in CDG-1m with variable symptoms, ranging from nonsyndromic dilated cardiomyopathy to multisystem manifestations.

Material and methods: A 15-year-old girl who has been followed up with a diagnosis of dilated cardiomyopathy was referred to pediatric gastroenterology unit for evaluation of diarrhea, anorexia, cachexia, nausea, regurgitation, abdominal pain, abdominal distension and fatigue. Her weight was 33.9 kg (-4.21 SD), height: 160 cm (-0.29 SD). She was the second child of first degree cousin Azerbaijanian parents. Her older sister who died at age of 14 had been followed up with heart disease with normal neurologic findings and had been operated for intestinal obstruction for 4 times. Laboratory and radiologic evaluation of the patient revealed anemia, mild acidosis, low levels of blood cholesterol and triglyceride levels and air-fluid levels on plain graphs. Results were leading to preliminary diagnosis as intestinal pseudoobstruction with probable mitochondrial neurogastrointestinal enteropathy. Genetic evaluation including next generation sequencing demonstrated a homozygous DOLK gene mutation N.1195C>G (p.Arg399Gly) (p.R399G) leading to the diagnosis of CGD type 1m. She is receiving supportive therapy for cardiomyopathy and treatment for gastroesophageal reflux disease and antibiotics for bacterial overgrowth.

Results: CDG can present with various clinical presentations. Cardiac manifestations as dilated cardiomyopathy has been reported in most of patients with CDG-1m. Also neurologic manifestations, limb anomalies, ichthyosis and pulmonary manifestations have been reported. Gastrointestinal manifestations are mostly presented as hepatic involvement.

Conclusion: This case presenting with features of intestinal pseudoobstruction is another example expanding the phenotypic spectrum of the CDG type1m.

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Peroral Endoscopic Myotomy (POEM) in children with achalasia: a literature review

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Objectives and Study: Paediatric achalasia is a rare neurodegenerative disorder of the oesophagus, characterised by incomplete lower oesophageal (LOS) relaxation and peristalsis of the oesophagus. Treatment is targeted at reducing LOS pressure. Peroral Endoscopic Myotomy (POEM) is an emerging and less invasive endoscopic alternative in comparison to the conventional surgical approach with excellent results in adults. The aim of this study was to determine efficacy and safety of POEM for the treatment of achalasia in children by literature review.

Method: A PubMed and EMBASE search of English literature was performed from inception to September 2017 using the keywords “children”, “achalasia” and “POEM”. Cohort studies &LT; 10 cases and studies describing patients > 18 years were excluded. Data regarding patient characteristics, treatment outcome and adverse events were extracted and presented descriptively, or pooled when possible.

Results: Two retrospective case-series and two prospective cohort studies evaluating POEM and one retrospective study evaluating POEM vs conventional achalasia surgery were included (n = 82, age 0.9 - 18 years). Follow-up ranged from 1 - 38 months, with reported success-rates of POEM ranging from 80% to 100%. Mean LES pressure and disease specific Eckardt symptom score decreased significantly in all studies. Twenty-two adverse events were reported, most importantly including one perforation and four pneumothoraxes. Four studies reported on the occurrence of post-operative gastro-oesophageal reflux disease (GORD) post-POEM, being present in 18/64 (25%) patients (follow-up ranging from 3 months to 3 years). Based on results of the study that compared POEM vs conventional achalasia surgery, no significant differences were found between both procedures in terms of post-operative symptoms and occurrence of adverse events. GORD was reported more frequently after POEM when compared to conventional surgery (33% vs 16%), albeit without statistical significance.

Conclusion: Based on results of the present review, POEM is a promising therapy for paediatric achalasia with very high success rates in terms of symptom relief. However, POEM may be associated with a high risk of developing GORD. Therefore, larger prospective studies are needed to confirm its efficacy and safety.

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Objectives and Study: The aim of this study is to assess the effectiveness and cost-effectiveness of adding physiotherapy to conventional treatment for children with functional constipation in primary care. Physiotherapy for functional constipation focuses on improving the coordination between the pelvic floor and abdominal musculature during bowel movements, while the focus of conventional treatment is on symptom relief. Therefore, we expect the effects of physiotherapy will be more sustainable than the effects of conventional treatment alone.

Method: We designed a randomised controlled trial (RCT) of children aged 4-17 years with functional constipation diagnosed by a general practitioner or pediatrician (Figure 1). Children in the intervention group received pediatric pelvic physiotherapy plus conventional treatment, and those in the control group received conventional treatment only. Participants were followed for 8 months, at which point the primary outcome ‘treatment success’ was measured. This was defined as the absence of functional constipation according to the Rome-III criteria in the past 4 weeks, with no laxative use. Secondary outcomes were treatment success at 4 months, treatment success irrespective of laxative use, quality of life, global perceived effectiveness, and costs. The sample size was calculated with expected treatment success rates after 6-12 months of 50% and 75% in the conventional and intervention groups, respectively. Given an expected loss to follow-up of 10%, we needed to include 128 children (alpha 0.05, power 0.80).

Results: Participants were recruited from September 2014 to February 2017. Initially, we aimed to include children with recent symptom onset; however, during enrollment, many children and their parents considered that the symptoms were not severe enough to justify physiotherapy. Therefore, we decided to expand our eligibility criteria to children with a longer duration of symptoms. Comparison of characteristics of children included in the RCT (participants, n=134) and children who refused to participate or fulfilled exclusion criteria (non-participants, n=90) showed that children using laxatives on a regular basis in the year before inclusion were most inclined to participate in the trial. In addition, participants were found to be slightly younger (mean age, 7.5 ± 3.46 years) compared with non-participants (mean age, 8.23 ± 3.80 years), but the boy-to-girl ratio was comparable.

Clinical impact: The results of this trial will provide valuable information for general practitioners and others involved in the treatment of children with functional constipation, and for stakeholders involved in clinical decision making. During enrollment, we discovered that children and their parents were often unwilling to accept physiotherapy at an early stage of the condition. This means that physiotherapy is probably not suitable as a standard treatment for children with recent-onset FC.

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Parent-child agreement on health related quality of life of children with functional constipation

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Objectives and Study: Health related quality of life (HRQoL) is an important outcome in clinical trials and important for clinical decisions regarding a child's treatment. Functional constipation has a major impact on the HRQoL of children and their families. Clinicians and researchers rely on a parent proxy-report and/or a child's self-report when they assess the HRQoL of a child. The question arises, are these two types of reports interchangeable? The aim of this study is to evaluate the parent-child agreement on HRQoL in children with functional constipation in general practice.

Methods: This study was designed as a reliability study that used baseline data of a randomised controlled trial on the (cost) effectiveness of physiotherapy in children, aged 4 to 17 years, with functional constipation. Children aged 8-17 years were eligible for this reliability study, because children below 8 years are too young to provide a self-report of their HRQoL. HRQoL was measured with the emotional and social functioning subdomains of the Defecation Disorder List (DDL, score 0-100), and the EuroQol™ 5-Dimension-Youth Visual Analogue Scale (EQ-5D-Y-VAS, scale 0-100) which measures health status. Parents completed a parent-proxy version of the questionnaires. The level of parent-child agreement on a group level was assessed with the Intraclass Correlation Coefficient (ICC) (two-way random model, single measures), with absolute agreement. An ICC of >0.90 was classified as "reasonable agreement for clinical measurements"; an ICC of 0.75-0.90 as good agreement; and an ICC of ≤ 0.75 as poor to moderate agreement. Bland-Altman plots were used to examine the level of agreement in individual parent-child pairs.

Results: Fifty-six children, median age of 10 years (IQR 8-12) were included. The level of parent-child agreement on a group level was good, with an ICC of 0.80 (95%-CI 0.67-0.88) for the DDL, and an ICC of 0.78 (95%-CI 0.65-0.87) for the EQ-5D-Y-VAS. Parent-child agreement regarding the DDL emotional functioning subdomain (ICC 0.73, 95%-CI 0.58-0.83) was slightly lower than the DDL social functioning subdomain (ICC 0.78, 95%-CI 0.65-0.87). Parents reported a minimally better HRQoL than their children, mean differences were -2.6±8.8 on the DDL and -2.9±12.6 on the EQ-5D-Y-VAS. Bland-Altman plots showed significant variation in the level of agreement between individual parent-child pairs. Limits of agreement were -19.7 and 14.6 for the DDL and -27.6 and 21.8 for the EQ-5D-Y-VAS. For the emotional and social functioning subdomains the limits of agreement were almost comparable (-23.9 and 19.5, and -24.2 and 18.3, respectively).

Conclusion: There is good parent-child agreement in the reported HRQoL on a group level. To assess HRQoL in a group of children with functional constipation, one can use either a parent proxy-report or a child self-report. However, the differences between individual parent-child pairs were sometimes of an order of magnitude that could be clinically meaningful. Therefore, we advise clinicians to assess the children's HRQoL in both the child and the parent. In case of discrepancies, the clinician could discuss the reason for this with the child and the parent. Future studies need to examine explanatory factors for disagreement between child self-reports and parent proxy-reports.

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**GASTROENTEROLOGY - GI motility, GERD and functional GI disorders**

**G-P-265**

**Increased incidence of infantile colics after neonatal antibiotics exposure and associated with increased immune markers at one year of age**

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**Objectives and Study:** The etiology of infantile colics is multifactorial but has been linked to compromised microbiota, and immaturity of the gut and immune system. Use of antibiotics after birth (neonatal AB) is associated with aberrant microbiota and immune development.

In a prospective cohort study, we determined whether neonatal AB increased the risk for infantile colics. In addition at one year of age, we compared circulating immune markers in children with and without infantile colics in the first 3 months of life.

**Methods:** A prospective observational birth cohort of 436 term infants was collected with 151 receiving broad-spectrum AB in the first week of life for suspected neonatal infection (AB+), and 285 healthy controls (AB-). AB+ was subdivided in treated for 48-72hr (AB2 (n=42)) and 7 days (AB7 (n=109)). In the first year, parents kept a daily diary for crying time (>3 hours yes/no) and monthly information on breastfeeding status. Infantile colics were defined according to the ROME III criteria. A forward multivariable logistic regression analysis was performed with correction for confounders (breastfeeding, tobacco exposure, delivery mode, siblings, family history of atopic disorders).

At one year of age, a blood sample was taken and analysed by multiplex immunoassay (84 cytokines/chemokines) based on Luminex technology in a subgroup (n=149). Children with (n=26) and without infantile colics (n=123) were compared with basic descriptive statistics. As this is an exploratory analysis, p<0.05 was considered significant. The trial was registered (NCT02536560).

**Results:** Infantile colics were more prevalent in AB+ than AB- (21.9% and 14.4% p=0.048; aOR 1.66 (95%CI 1.00-2.77)), being significant in AB7 only (24.8%; p=0.015). Duration of breastfeeding and delivery mode did not differ in children with and without infantile colics.

At one year of age, 10/84 circulating immune markers were significantly increased (p<0.05): IL-31, LIGHT, YKL-40, CXCL13, sPD1, IL1RI, sIL-7Ra, Gal-1, Gal-9 and S100A8 in children with infantile colics (n=26) compared to children without infantile colics (n=123). At least four of these markers (IL-31, Gal-1, Gal-9, S100A8) are associated with intestinal inflammation.

**Conclusion:** Exposure to neonatal antibiotics (7 days of treatment) increases the risk for infantile colics. At one year of age, children that suffered from infantile colics in the first 3 months of life had increased intestinal related inflammatory markers (including IL-31, Gal-1, Gal-9, S100A8). This suggests long term consequences of infantile colics which might predispose these children for future functional gastrointestinal disorders (FGID). Follow-up of this cohort may give insight in the risks of both neonatal antibiotics and infantile colics for FGID.

**Disclosure of interest:** B. van’t Land, J. Garssen, R.M. van Elburg are employees of Nutricia Research Utrecht. The study was, in part, financially supported by Nutricia Research.

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**Sacral nerve stimulation versus antegrade continence enema treatment for children with intractable constipation and fecal incontinence**

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**Objectives and Study:** Treatment options for children with intractable functional constipation (FC) and fecal incontinence (FI) are limited and include sacral nerve stimulation (SNS) and antegrade continence enema (ACE) treatment. No studies have compared these two treatments. The objective of this study was to compare the efficacy of SNS and ACE treatment for children with intractable FC and FI.

**Method:** We performed a retrospective cohort study. We included children 6-18 years old with FC based on Rome IV criteria and FI who were treated with either SNS or ACE at our institution from 2012-2016. We excluded children with organic causes of constipation or with prior abdominal surgery. We recorded demographic information, medical history, and symptoms at baseline, 6 months, 12 months, 24 months, and at the most recent visit after starting SNS or ACE treatment. We compared improvement in FI, bowel movement (BM) frequency, abdominal pain, and laxative use at each follow up time point between patients treated with SNS and ACE. We also recorded complications.

**Results:** We included 19 patients treated with SNS (73.7% female, median age 10 years at treatment initiation) and 23 patients treated with ACE (52.2% female, median age 10 years at initiation). The most recent visit was a median of 22 months (range 3-52) after treatment initiation. All patients had symptoms of FC for >12 months (median 66 months) and were treated with oral laxatives before SNS or ACE. Improvement in FI was greater with SNS than ACE at 12 months (92.9% vs. 57.1%, p=0.03) and 24 months (100% vs. 57.1%, p=0.02). Improvement in BM frequency and laxatives use was greater with ACE at all time points (all p< 0.05). At the most recent visit, 82.4% of SNS patients had >2 BMs per week versus 95.7% of ACE patients (p=0.00). Improvement in abdominal pain was greater with ACE at the most recent visit (45.5% vs. 7.7%, p=LT; 0.05). Overall complications were more common in the ACE group compared to the SNS group (82.6% vs. 26.3%, p=LT; 0.01), however rate of patients with complications requiring surgery was similar between SNS and ACE (26.3% vs. 21.7%, NS).

**Conclusion:** In the first comparison of SNS and ACE, we found that both SNS and ACE led to durable improvement in FC and FI symptoms. SNS may be more effective in treating retentive FI, but ACE clearly led to greater improvement in BM frequency. Prospective studies are needed to determine the optimal treatment strategy for children with intractable FC and FI.

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Epidemiology of functional defecation disorders in children, a systematic review and meta-analysis

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Objectives and Study: Functional defecation disorders (FDDs) comprise functional constipation (FC) and functional non-retentive fecal incontinence (FNRFI). Our aim was to systematically review the literature regarding the epidemiology of FC and FNRFI in children according to the Rome criteria. Secondary objectives were to evaluate the sex, age and geographic distribution of FC and FNRFI and evaluate associated factors.

Method: The Cochrane Library, Pubmed and EMBASE databases were searched from 2006 until September 2017. The following inclusion criteria were applied: (1) prospective studies of population-based samples; (2) reporting on the prevalence of FC or FNRFI according to the Rome III or IV criteria; (3) in children aged 0-18 years; (4) published in full manuscript. Random effect meta-analyses with meta-regression analyses of study characteristics were performed.

Results: Thirty-five studies reported on the prevalence of FC and 15 studies described the prevalence of FNRFI. The prevalence of FC ranged from 0.5%-32.2% with a pooled prevalence of 9.5% (95% CI 7.5-12.1). The reported prevalence of FNRFI ranged from 0.0%-1.8%, with a pooled prevalence of 0.4% (95% CI 0.2-0.7). For FC, pooled data analysis did not reveal differences related to sex (8.6% in boys vs. 8.9% in girls, OR 0.99) or age. Geographical location, dietary habits and exposure to stressful life events were reported to be associated with the presence of FC. No associated factors were identified for FNRFI.

Conclusion: FDDs are common in childhood. Geographical location, lifestyle factors and stressful life events are associated with FC.

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FLNA loss-function-mutation contributes to the intestinal retardation and obstruction

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**Objectives and Study:** A Congenital short bowel syndrome (CSBS) is a rare congenital gastrointestinal disorder with significant morbidity and mortality in pediatric patients. However, it was unknown that the underlying genetic cause of this congenital disease.

**Methods:** The extracted DNA from the peripheral blood for whole-exome sequencing, followed by targeted Sanger sequencing. Full-thickness biopsy findings were analysed by hematoxylin & eosin (H&E) staining, Alcian blue/periodic acid-Schiff (AB/PAS) and immunohistochemistry (IHC).

**Results:** We here found a stop-gained mutation (c.79G>T) in filamin A (FLNA) in a male CSBS patient using whole-exome sequencing and targeted Sanger sequencing. This mutation located at the first exon of FLNA and lead to FLNA stop-translation from the position of the 27th amino acids (p. Glu27*). Indeed, the immunohistochemical investigation revealed an apparent defect of the FLNA protein in the CSBS patient. Moreover, full-thickness biopsy findings showed the patient had degeneration of intestinal smooth muscle and some hyperganglionosis. Functional analysis indicated that stop-gained mutation in FLNA or FLNA knockdown significantly inhibited the growth and contractility of intestinal smooth muscle cells (ISMCs).

**Conclusions:** Taken together, our findings suggested that Glu27* variant in the FLNA could cause the intestinal retardation and obstruction.

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GASTROENTEROLOGY - GI motility, GERD and functional GI disorders

G-P-270

Gastroesophageal reflux disease and childhood asthma

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Objectives and Study: Gastroesophageal reflux disease (GERD) is common in children with asthma. The connections between bronchial asthma (BA) and GERD remain unclear, some researchers suppose that antireflux medications can help asthma symptoms. The main objective of our study was to establish links between bronchial asthma and symptomatic gastroesophageal reflux disease and to evaluate the impact of GERD treatment on the severity of BA.

Method: 23 patients (group 1) with BA and GERD, admitted to the Department of allergic diseases, and 18 patients (group 2) with GERD and established BA, admitted to the Department of Gastroenterology in 2017, were examined. Patients were assigned to upper endoscopy and pH monitoring, pulmonary function testing, IgE levels. Both groups have been treated with omeprazole (1,0-2,4 mg/kg/day) for 3 months, followed by pulmonary function testing. Mean age was 7,9 (group 1) and 8,12 (group 2), males predominated in all groups.

Results: Evaluation of BA severity revealed that children in group 1 were more likely to have severe and moderate asthma (60,7%; p&LT; 0,01), mixed-type (43,5%; p&LT; 0,05). Severe forms of GERD, including erosions, were also significantly more frequent in group 1 (34,7%; p&LT; 0,01). In second group 72,2% of children had GERD without endoscopic esophagitis (p&LT; 0,05). In both groups (87,0% and 83,3%) the diagnosis of asthma preceded the diagnosis of GERD. Allergic or mixed sensitization (according to IgE levels) was established in most of patients (87% in group 1 and 72,2% in group 2). After 3 months of treatment with omeprazole 85.3% of children in both groups reported a reduction in the incidence and severity of GERD symptoms. In 17,1% of cases an improvement in pulmonary function testing was established.

Conclusion: There is a correlation between the severity of BA and symptomatic GERD. The leading role in the development of the combined pathology of bronchi and the esophagus belongs to allergy. Treatment with omeprazole may improve the course of BA in 17,1% of patients.
Eosinophilic Esophagitis in Children: a favorable response to combination therapy with elimination diet and proton pump inhibitors

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Objectives: Eosinophilic Esophagitis (EoE) is a chronic immune-mediated primary esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. It is a rare disorder, but the incidence is rising dramatically over the past decade. EoE involves genetic, environmental and immunologic components. Clinical manifestations vary with age, most are non-specific, thus offering a diagnostic challenge. Atopic diseases are a comorbidity. Diagnosis is based on the presence of > 15 eosinophils in a high power field (HPF) in esophageal biopsy. Proton Pump Inhibitors (PPIs) are a first line therapy, followed by an elimination diet, guided by allergic essays. Steroids, both topical and systemic offer an alternative but entails adverse reactions. We present out experience of an EOE allergy and gastrointestinal multidisciplinary clinic during a 5 years period 2010-2015.

Methods: A descriptive and retrospective analysis of a cohort of 30 consecutive children with full EOE diagnostic criteria, full allergic evaluation with skin prick tests (SPT) and atopy patch tests (APT), and clinical and histological data. Biopsy data were collected and a questionnaire regarding symptoms, therapy and course of the disease conducted and analyzed.

Results: Bimodal peak age of onset was 0-2 and 9-12 years. Average time to diagnosis was 1.46 years. Feeding difficulty in infants and dysphagia in older children were the most common presenting symptom. The two main age groups showed significant differences in time to diagnosis. Feeding difficulty, vomiting and failure to thrive in the younger age led to prompt investigation and diagnosis, while nonspecific gastrointestinal complaints of abdominal pain in older children led to a longer time to diagnosis. Most had a family and personal history of atopy, asthma being the most prevalent (57%). The most common allergens found in Skin Prick Tests (SPT) were house dust mite, peanuts (40%), milk (20%) and eggs (12%). At diagnosis the average number of eosinophils per HPF was 70.47, eosinophil microabscesses and basal cell hyperplasia were found in 50% and 92% respectively. The most common therapy was elimination diet (90%) alone or in combination with other treatments. A combination of proton pump inhibitors (PPI) and elimination diet in 31%, a combination of PPI elimination diet and swallowed topical steroids in 38%. Overall PPI were given in 60%, swallowed topical steroids (Fluticasone, Budesonide) in 40%. A minority (20%) required systemic steroids and one patient required endoscopic dilations. 70% were offered more than one treatment modality. 80% underwent repeat biopsy to follow up on treatment response or after reintroduction of foods. 77% reported relief of symptoms, 83% of those who underwent repeat biopsies demonstrated a significant histological improvement.

Conclusions: EoE in children is a diagnostic challenge, requiring a high level of clinical suspicion due to its non-specific symptomatology. In our cohort, an elimination diet resulted in high success rate, but requires extensive support for patients and families. Further studies are required to determine disease course, establish prognosis and characterize the morbidity in adults who presented while young.

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Definitions and outcome measures in pediatric functional abdominal pain disorders: a systematic review

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Objectives and Study: Functional abdominal pain disorders (FAPDs) are common in children and associated with significant impact on quality of life, school absence and high economic burden. Pathophysiology underlying these disorders is thought to be multifactorial but remains largely unclear, which limits successful uniform evidence based clinical management. We hypothesized that definitions and outcome measures in randomized controlled trials (RCTs) on pediatric FAPDs would also be heterogeneous. Therefore the aim of this study was to systematically assess definitions and outcome measures in therapeutic RCTs in children with FAPDs.

Method: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL databases were systematically searched from inception to March 2017. A study was included if it was an English-written therapeutic RCT or systematic review concerning FAPDs in children from 4-18 years old. Quality was assessed using the Delphi List. Data were tabulated and presented descriptively.

Results: A total of 4511 unique articles were found of which 61 articles were included. Twenty-four (39%) studies were of high methodological quality. Individual FAPDs were defined in 15 different ways (median 1.5, range 1 - 9). Most studies used the Rome III (48%) or II (16%) criteria. Fourteen studies (23%) assessed a pharmacological, 23 (38%) a dietary, and 24 (39%) a psychosocial intervention (total 25 different interventions). Thirty-six (59%) studies predefined the reported primary outcome measures in their methodology. In total, 87 different primary outcomes were reported, measured by using 18 different clinical parameters. The individual parameters of pain intensity, frequency and severity were used most often (in 57%, 57%, and 20% of studies, respectively). Of the 14 studies that evaluated a pharmacological intervention, 12 (86%) reported on side effects, of which 6 (43%) included this as a predefined outcome measure.

Conclusion: Heterogeneity and inconsistency exist in definitions and outcome measures used in RCTs on pediatric FAPDs. To improve comparison between future studies, we recommend the development of a standardized set of core outcomes for therapeutic RCTs in children with FAPDs.

Disclosure of interest: M.A. Benninga is a scientific consultant for Shire, Sucampo, Astrazeneca, Norgine, Zeria, Coloplast, Danone, Friesland Campina, Sensus, Novalac. The authors report no other relevant potential conflicts of interest.

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Clinical and epidemiological characteristics of Cryptosporidium spp. infections in paediatric patients in France, 2015-2017

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Objectives and Study: In children, the prevalence of cryptosporidiosis, a common cause of parasitic diarrhoea, appears to be frequently underestimated. The aim of the study was to establish clinical and epidemiological characteristics of cryptosporidiosis cases in paediatric patients from metropolitan and overseas France reported from January, 2015 to November 2017 to the CryptoANOFEL network.

Methods: Cases were notified by 41 tertiary hospitals and 3 private French Parasitology laboratories with detailed clinical/epidemiological data and individual stool samples. Cryptosporidium spp. oocysts were detected by staining and immunomagnetically purified. Isolate species/genotypes were determined by PCR amplification/sequencing of SSU RNA and gp60 gene fragments.

Results: From January, 2015 to November, 2017, 96 children (49 male, 47 female) were reported of which 74 and 22 were immunocompetent and immunodeficient, respectively. Cryptosporidiosis occurred mainly from July to October (60/96 cases). Of 26 patients for whom duration of symptom was recorded, 25 exhibited symptoms which lasted more than one week. A potential risk factor was identified for 49/96 patients: contacts with household, child care and school diarrhoea cases (22, 1 and 2 cases, respectively), or recreational water activity, water drinking from uncontrolled well, seafood or non pasteurized milk (15, 3, 3 and 2 cases, respectively). Most (85%) patients presented diarrhoea, associated with fever, vomiting, abdominal pain, weight loss, and dehydration in 29%, 29%, 25%, 20%, and 20%, respectively. Fifty five patients were hospitalized. In neonates, *C. hominis* was more frequently detected than *C. parvum* (3/5 cases) while on the contrary, *C. parvum* infection was twice more prevalent in children aged from 2 to 5 years old and represented more than 80% in children older than 5. No difference in symptoms was noted between *C. hominis* and *C. parvum* cases. Fifty four children received no therapy, while 10, 10, 14, 6, 3 and one were treated by parenteral rehydration, oral rehydration, nitazoxanide, anti diarrheal drugs, antibiotics and reduction in immunosuppressive dose regimen, respectively.

Conclusions: Present results indicate that symptomatic cryptosporidiosis was common in the French paediatric population, especially in immunocompromized patients. Possible risk factors were frequently identified and hospitalization was required in more than half cases. *C. hominis vs C. parvum* representation depended on age. Data underline the importance of early diagnosis of paediatric cryptosporidiosis cases to optimally manage a potentially severe condition.

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Assessing the compliance with the guidelines for acute gastroenteritis management in children

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Acute gastroenteritis (AGE) remains a major cause for visiting the emergency department (ED) by infants. In 2008, ESPGHAN and ESPID jointly developed evidence-based guidelines for its approach.

Objectives and Study: The main aim of this study was to evaluate the compliance with these recommendations for the treatment of AGE in children in the outpatient setting and to identify the leading reasons for their violation.

Method: A prospective study was conducted in two hospitals in the north of Portugal. Information was collected through questionnaires filled out by the caregivers of children who went to the ED with symptoms of AGE. There were two moments of enquiry: at the time of hospital admission and one week later. The questions concerned: the therapy performed at home, performed in the ED and the therapeutic measures recommended at the time of medical discharge. The main outcome was the proportion of children managed in full compliance with the guidelines. The vaccine coverage against rotavirus was also determined.

Results: There were 81 children included in the sample. The guidelines were strictly followed in 47.5% of children and oral rehydration solution (ORS) was used in 90.2%. There was a greater adherence to the guidelines in younger children (p = 0.032): 59% of children managed in full compliance with the guidelines in the group with 3 or less years comparing to 28.6% of children older than 3. The most common violations were dietary changes (44.3%), restriction of dairy products (39.7%) and use of additional drugs (39.3%). 53.1% of parents knew that ORS is the major treatment of AGE. There was an association between caregivers higher educational level and knowledge about ORS (p = 0.02). Children whose usual dietary pattern did not suffer any changes had a shorter period of diarrhoea (p = 0.046). Probiotics were used in 44.3% of the cases. The difference found in the duration of the symptoms in children using probiotic (Md = 3) and those who didn’t (Md = 2) was not significant (p = 0.369). A vaccine coverage of 65.5% was obtained but there was no significant difference in the median duration of the symptoms between vaccinated and non-vaccinated children (p = 0.707). In 29 cases (47.5%) the caregivers say that they feel capable to treat their child at home in case of a future similar episode.

Conclusion: Considering that only half of the children were treated in full compliance with the guidelines, there is a need to improve their diffusion and implementation. An educational intervention in the community could enhance parents' knowledge about managing AGE and reduce ED visits. Regarding medical practice in conformity with the recommendations, dietary changes and abuse of prescription are the most likely factors to be improved. Following the recommendation of maintaining the usual diet reduces the duration of the diarrhoea.

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Comparison of Helicobacter pylori stool antigen positivity and H.pylori presence in gastric mucosal biopsies in patients with dyspeptic symptoms

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Objectives and Study: H. pylori infection is spread worldwide and infects at least 50% of the world's population. The route of transmission is not known, but is suggested to be faecal-oral or oral-oral. H. pylori infection may be acquired during childhood, and especially in developing countries it may be acquired as early as in infancy. There are limited guidelines regarding its diagnosis in children and adolescents. Several invasive and non-invasive tests are available to detect, but no ideal test is found. The definitive diagnosis is still made only by endoscopy with multiple biopsy specimens obtained from two or more regions of the stomach. Testing of H. pylori antigens in stools has shown promising results in adults, but in children insufficient data are available to confirm the accuracy of H. pylori stool antigen test (SAT).

Method: Children between 3-18 years with abdominal pain, dyspeptic complaints and severe epigastric tenderness were evaluated. H. pylori antigens in stools was asked from all children. Upper GI endoscopy was done for symptomatic children for whom organic cause was proposed. Total 238 patients between March 2015 and March 2016 retrospectively were evaluated. Patients who previously had treatment for H.pylori or who take PPI and/or antibiotics at least 2 weeks before were not included. Fresh stool specimen was used for immunochromatographic strip test (True line H.pylori Stool Ag kacet Test, Biocare diagnostics), gastric mucosal biopsies were taken from antrum (two) and corpus (two) and evaluated according to Sidney classification. Results from H. pylori antigens in stools and from stomach biopsy specimen were enrolled. Descriptive statistical tests were expressed as mean ± standard deviation. Stool H. pylori Ag were expressed as positive or negative, sensitivity and specificity were calculated. The threshold of significance set at P < 0.05.

Results: The average age of the patients was 13 years (±3.9), (3.1-17.9 years). Of all patients, 63% were above 12 years and 30% between 6-12 years, and the rest 3-6 years. Ratio of females was 63.9% and males 36.1%. H. pylori stool Ag was positive only in 8% of all patients. SAT was negative in all patients below 6 years of age. In 51.7% of the patients stomach biopsies was positive for H.pylori and 18% of these patients had peptic ulcer disease. Biopsies were positive for H.pylori in 85% of children with antral nodularity. SAT sensitivity was only 15% and specificity was 100%. There was a statistical significance between stool antigen test and stomach biopsies for H.pylori (p< 0.01).
**Conclusion:** SAT is cheap, non-invasive test, used widely for primary diagnosis and for the assessment of eradication therapy. 13C-, or 14C-urea breath tests are best, but are more expensive, difficult to apply to non-compliant children, and have an uncertain cut-off and also not available in our country. Stomach biopsies seem to be the gold standard for diagnosis of H.pylori infection in children.

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GASTROENTEROLOGY - GI-infections

G-P-277

Altered gut microbiota in preterm newborns with necrotizing enterocolitis using High-Throughput sequencing

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Objectives and Study: Recent studies have shown that pathophysiology of necrotizing enterocolitis (NEC) includes intestinal microbial dysbiosis and mucosal barrier disruption. This study tends to investigate intestinal microbiota in preterm newborns with NEC.

Method: Our prospective study enrolled 24 preterm newborns admitted to the NICU in Shanghai Children's Medical Center from March 2013 to August 2014, whose gestational age ranged from 29 to 33 weeks. Among the 24 preterm, 4 were diagnosed as NEC, while 3 were treated with antibiotics due to serious infections (infection group) and 17 without any infectious complications (normal group). Totally 192 longitudinal fecal samples were collected right from admission until discharge day. The Intestinal microbiota composition and its longitudinal trend were analyzed using Illumina-MiSeq high-throughput sequencing.

Results: At phylum level, Firmutes and Proteobacteria dominated respectively in three groups, while Proteobacteria abundance of NEC group significantly ranked first (NEC vs Infection vs Normal: 59.84% vs 42.97% vs 44.13%, p=0.048). At class level, three groups shared the same domination microorganisms which are Bacilli, Clostridia and Gammaproteobacteria, and Gammaproteobacteria abundance of NEC group is significantly the highest (NEC vs Infection vs Normal: 53.63% vs 33.96% vs 39.46, p=0.018).

Longitudinal comparison showed different microbial colonization pattern among three groups. Notwithstanding the same microbial development mode shared by three groups from Bacilli to Gammaproteobacteria within two weeks after birth, Bacilli and Clostridia domination from the 14th to 30th day of life and Clostridia domination after the 30th day of life in NEC group was distinctive and noticeable.

Conclusion: Abnormal intestinal microbiota at early life might account for NEC. However, more longitudinal studies with larger sample sizes are needed to reveal microbial dysbiosis at different stages before and after the onset of NEC, hopefully to provide evidence for its early recognition and prevention.

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Risk factors and treatment options for prolonged diarrhea in children: an observational comparative study

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Objectives and Study: Prolonged diarrhea (ProD) is defined as acute-onset diarrhea lasting 7 or more days (but less than 14). It was previously defined acute-protracted diarrhea and occurs in 7-11% of children hospitalized because of acute gastroenteritis (AGE). Pathogenesis, etiology and management of ProD are still undefined. An observational study was carried on in 2 pediatric hospitals to investigate etiology, risk factors, clinical features, management and outcome.

Method: All children accessing hospital with diarrhea lasting between 7 and 14 days were enrolled. Clinical features, diagnostic and therapeutic interventions were recorded during hospitalization and persistence of diarrhea was investigated one month later through a telephone call. Age-matched children with AGE lasting less than 7 days were enrolled as control group.

Results: A total of 43 children with ProD were enrolled (median age 23.5 months, IQR 21.6, M:25), with a mean time of hospital stay of 12.6 days and a mean duration of diarrhea of 14.3 days; 56 children with GE (median age 19 months, IQR 21.6, M:25) served as control. Etiology of ProD was identified in 15/43 (35%) of children, with 13 infections (7 viral, 5 bacterial, 1 parasitic), 1 malrotation, 1 ulcerative colitis. 18 children (42%) met the definition of chronic diarrhea (duration >14 days) but only 1 child still had diarrhea 1 month after enrollment. Preterm birth, age, gender, ethnicity, breastfeeding, time of weaning, hospitalization in the last month, history of allergies, malnutrition, immunodeficiency or other underlying chronic conditions were equally distributed among children with ProD and AGE. Antibiotic therapy in the previous month (34% vs 17%) and use of a formula (21% vs 5%) or mixed feeding (10% vs 0%) were more frequently reported in children with AD than those with ProD (p=0.02). Although the degree of dehydration was similar, the rate of children presenting weight loss >5% significantly varied according to duration of diarrhea: AD (20%), ProD (42%) and chronic diarrhea (69%, p=0.001). Children presenting with >5 stools/day had a significantly higher risk of ProD (OR 3.3, 95%CI 1.3-8.3). Treatment of children with ProD included probiotics (77%), antibiotics (53%), lactose-free diet (23%), hydrolyzed formula (7%), oral immunoglobulins (5%), and parenteral (4%) or enteral nutrition (2%). Children receiving probiotics showed a significant reduction in duration of diarrhea if compared to those not receiving probiotics (12.7 vs 21.1 days, p=0.02). LGG was the strain used in most of cases (28%).

Conclusion: Children with ProD frequently present more episodes of diarrhea at its onset and weight loss correlates with longer duration of diarrhea. Infectious diarrhea is the most common etiology detected in children with ProD, but ProD may be the onset of chronic intestinal diseases. Probiotics may have a role in the treatment of children with ProD, but more data are needed to confirm this finding.

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Plant extracts efficiently decrease the adhesion of Campylobacter jejuni to human and animal intestinal epithelial cells

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Objectives and Study: Campylobacter jejuni is one of the most common bacterial causes of diarrhoea in the industrialised world. To establish an infection, campylobacters must first attach to and persist in the mucus layer that covers the intestinal epithelium, and they need to survive the adverse conditions of the gastrointestinal tract. Targeting the attachment can eliminate infection at the early stages. An alarming increase has been seen in the prevalence of antibiotic-resistant bacterial strains, such as Campylobacter and for that reason it is important to develop strategies to control these infections without the use of antibiotics. Plants present a valuable source of bioactive compounds that might target Campylobacter adhesion and have a great advantage in combating infections without selection pressure for the emergence of resistant bacteria, while also not causing deleterious effects to the host microbiota. Furthermore, there are huge quantities of by-products and waste materials in the agro-food and pharmaceutical industries, which are a valuable source of bioactive phytochemicals and could be re-used. Therefore, the aim of our study was to evaluate different plant extracts/waste material for their anti-adhesion activity.

Method: We initially determined the antimicrobial activity and cytotoxicity of chemically characterized extracts from waste skins and seeds of Pinot noir grapes (GSS), thyme (TE) and its hydrodistillation residue (TE-R), olive tree leaves (OE), as well as Alpinia katsumadai seed extract (SEE) and its hydrodistillation residue (hdSEE-R) against pig (PSI) and human foetal small-intestinal epithelial (H4) cell line, to avoid any influence in antiadhesion testing. The effects of these extracts on adhesion, invasion, and intracellular survival of the poultry meat isolate C. jejuni K49/4 in the PSI and H4 cells were determined. One-way ANOVA followed by Dunnett's multiple comparison tests was performed to compare the C. jejuni counts between the control and test extracts in the anti-adhesion assays.

Results: We showed that the OE, TE, TE-R, SEE and hdSEE-R are effective for inhibition of C. jejuni adhesion, and thus for biofilm formation, although they did not inhibit C. jejuni growth or kill C. jejuni cells at concentrations tested for their anti-adhesion activity (0.2-50 µg/ml). Our results demonstrated reduced C. jejuni adhesion up to 30% with extracts (TE and SEE) and interestingly, also with their waste material. The SEE and hdSEE-R extracts showed strong anti-adhesion activities against C. jejuni for the PSI cells even at very low concentrations. The anti-adhesion activities of these extracts were stable across a large concentration range.
**Conclusion:** Although a standard treatment for *Campylobacter* infections is well established, it is urgent to search for new options to combat infections without the use of antibiotics. In our study we presented an alternative strategy that uses low doses of bioactive phytochemicals for the safe control of *Campylobacter* by targeting their adhesion properties. Presumably through blocking receptors and bacterial adhesins or inhibition of essential bacterial enzymes these extracts have a potential use in prophylaxis for prevention and treatment of *Campylobacter* infections.

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An enzyme-linked immunosorbent assay for diagnosis of intestinal capillariasis in children

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Intestinal capillariasis caused by Capillaria philippinensis is manifested as chronic diarrhea and malabsorption which, if untreated, may result in death. Multiple stool examinations may be unable to accurately identify this parasite. This case report aimed to demonstrate the use of an enzyme-linked immunosorbent assay (ELISA) for detection of antibodies against C. philippinensis in patient with negative conventional stool examinations.

A 8 year-old-girl from the northeast of Thailand was presented with chronic diarrhea for a year. She also had facial and lower limb swelling with scaly dermatitis of both legs. She had no fever or abdominal pain but had weight loss of 9 kg in one year. Additional history she regularly consumed raw or undercooked food from fresh water fish known as “Koi Pla”. Investigation revealed anemia with a hemoglobin of 10 g/dL and absent peripheral eosinophilia. She had profoundly protein losing enteropathy with albumin and globulin 1.4 and 2 g/dL, respectively with negative proteinuria. Multiple stool examinations included stool concentration revealed no ova, cysts or parasites. She underwent upper gastroduodenal endoscopy and colonoscopy that were macroscopically normal and microscopically mild gastritis and colitis with some scattered eosinophilic infiltration. She was diagnosed of intestinal capillariasis following positive antibodies against C. philippinensis by ELISA and treated by oral albendazole for 28 days. Her clinical of diarrhea and dermatitis were improved in 14 days post treatment and finally regained weight in one month.

The use of ELISA for diagnosis intestinal capillariasis seems to be a promising investigative method in patients with negatives result of multiple conventional stool examinations and/or microscopically intestinal specimen.

Keywords: capillariasis, enzyme-linked immunosorbent assay, children

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Anthropometric measures in adolescents with inflammatory bowel disease: a population based study

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Objectives: Growth impairment is common in paediatric inflammatory bowel disease (IBD) patients. Nevertheless, a controversy exists regarding disease impact on final adult height. We investigated the impact of IBD on anthropometric measures, including weight, height and body mass index (BMI), at late adolescence in a cross-sectional, population based study.

Methods: A total of 1,144,213 Jewish Israeli adolescents who underwent a general health examination from 2002 to 2016 at a median age of 17.1 years (interquartile range 16.9-17.4) were included. IBD cases were stratified into Crohn’s disease (CD) and ulcerative colitis (UC). Patients were also sub-grouped based on age at IBD diagnosis.

Results: Overall, 2,372 cases of IBD were identified out of 1,144,213 persons examined (0.2%). CD accounted for 68% of IBD cases. Both UC and CD patients (males and females) had significantly lower weight and BMI compared with controls. Differences in near-final height were not statistically significant for either diseases compared to controls (Females: 162cm vs 161.8cm vs 161.5cm; Males: 174cm vs 173.8cm vs 173.6cm for controls, UC and CD, respectively).

Subgroup analysis showed that only patients with CD who were diagnosed at age<14 years were significantly shorter than controls (Females: 162cm vs 160.6 cm, p=0.01; Males: 174cm vs. 172.7cm, p<0.01, for controls and CD, respectively). This difference widened as the age at CD diagnosis decreased. Compared with controls, the proportion of both UC and CD patients with short stature (height<LT; 3rd percentile) was significantly higher for males with both diseases (4.3% vs 5.7% vs 5.6%, p=0.02) but not for females (4.3% vs 6.1% vs 5.6%, p=0.09 for controls, UC and CD, respectively).

The proportion of CD patients with malnutrition (BMI<LT; 3rd percentile) was significantly higher compared with UC and controls (Females: 2.8% vs 2.9% vs 3.4%, p=0.017; Males: 3.8% vs 3% vs 5.3%, p<0.001 for controls, UC and CD, respectively).

Conclusion: IBD adolescents were leaner compared with the general population. No overall difference was noted in near-final height. Younger age at diagnosis is associated with reduced near-final height with a linear correlation between age at diagnosis and near-final height. Short stature is more prevalent in males with either UC or CD compared with controls whereas malnutrition is more prevalent only in CD patients from both genders.

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Objectives and Study: Ulcerative colitis (UC) is thought to result from an aberrant immune response. Interleukin (IL)-23/T-helper 17 pathway and Forkhead box P3 (FOXP3) regulatory T (Treg) cells play an important role in the pathogenesis of inflammatory bowel disease, but little is known about their role in children with UC. The aim of this study was to investigate the role of IL-23 and FOXP3 in the pathogenesis of UC by determining them in intestinal tissues of children with the disease.

Method: We studied 29 patients with UC (18 pancolitis, nine left-sided colitis, and two proctocolitis) and 11 control subjects. Immunohistochemistry was used to examine IL-23 and FOXP3+ Treg cells in intestinal biopsy specimens from UC patients and from non-inflamed tissues in the control group.

Results: The incidence of IL-23 and FOXP3+ Treg cells was higher in patients with UC compared to the control group. IL-23 and FOXP3+ Treg cells expression in patients with pancolitis were higher than in the control group. However, no differences were determined in IL-23 and FOXP3+ Treg cells in patients with left colon involvement and proctocolitis compared to the control group.

Conclusion: IL-23 and FOXP3+ Treg cell expression were higher in the intestinal mucosa of children with UC. These data indicate that new therapeutic options directed toward inhibiting the IL23 pathway and raising Treg cell numbers may permit more efficacious treatment of UC.

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Inflammatory bowel disease in Omani children

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Objective: Report the burden of disease of IBD in Omani children with their demographic and clinical characteristics.

Methods: Retrospective observational study of all children seen in the Royal Hospital with diagnosis of IBD from the period of January 2010 till November 2017. All patients’ data were retrieved from the electronic records including bio-demographic and clinical parameters. Data were analyzed using Excel spreadsheet software with means, medians were calculated as appropriate. Student t test was used for P value calculations.

Results: There were 22 children identified 10 of them being females and 12 males. The mean age of diagnosis was 9 years while the youngest child was 1.6 years. Eleven children had ulcerative colitis (UC) and another 11 children had Crohn’s disease (CD). Abdominal pain and bleeding per rectum was more common in UC patients compared to CD while weight loss was more common in CD. There was no significant difference between age of onset, Hb or albumin in children between UC or CD in Omani children. Biological therapy was equally needed in both group with no difference either. The mean Hb for the whole group was 9.1 g/dl, albumin of 29.4 g/l, CRP of 42 g/l and ESR of 46 g/l.

Conclusion: IBD in Omani children remains an uncommon disease with equal burden between UC and CD. Further studies are needed to look at the possible factors keeping the disease burden in Oman low compared to other neighboring countries.
The role of inflammation in the endothelial dysfunction in a cohort of paediatric Inflammatory Bowel Disease patients

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Objectives and Study: Chronic inflammation plays a central role in the etiology of endothelial damage. Endothelial dysfunction is the inability of the artery to dilate in response to an endothelial stimulus. We assessed the endothelial dysfunction (ED) by measuring the reactive hyperemia index (RHI) and the flow-mediated dilation (FMD) in a cohort of paediatric patients affected by Inflammatory Bowel Disease (IBD) and comparing these parameters to a group of healthy controls (HC).

Method: Forty-one patients were consecutive enrolled. ED was evaluated by both the plethysmographic RHI method and the measurement of the FMD of brachial artery after occlusion of the blood flow. Differences between patients and controls were assessed by the Mann-Whitney test. In each IBD patient, the main inflammation markers were detected and correlated to RHI and FMD by a linear regression test.

Results: We enrolled 23 (56%) IBD patients and 18 (44%) HC. When comparing FMD value at diagnosis it was significantly lower in IBD patients than in HC (p=0.05). This result was confirmed at follow-up, when this difference became even more significant (p=0.003). A significant indirect correlation was found between FMD and fecal calprotectin (r²=0.17;p=0.04). No differences were found when comparing RHI.

Conclusion: Our results show how inflammation could lead to endothelial dysfunction assessed by ultrasound flow-mediated dilation (FMD). These data were not confirmed by RHI, however this could be due to the lack of a standardized paediatric cut-off. More studies are necessary to confirm our data.

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First faecal microbiota transplantation in paediatric inflammatory bowel disease in Italy: a pilot study

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Objectives and Study: Management of Paediatric Inflammatory Bowel Disease (PIBD) is a challenge in clinical practice, due to possible failure of available treatments, frequent complications and long lasting disease. As the gut microbiota plays an important role in intestinal homeostasis, its modulation with Faecal Microbiota Transplantation (FMT) could represent a valid strategy in selected patients.

Methods: The first pilot study about FMT in Italy has been developed at Bambino Gesù Children's Hospital (OPBG) in Rome, for PIBD. Main objectives are feasibility and safety. Secondary objectives include the analysis of faecal microbiota, and the characterization of mucosal and peripheral immune pattern.

Inclusion criteria are diagnosis of PIBD, age 6-18, mild-to-moderate disease (10< PUCAI< 65, 12.5< wPCDAI< 57.5), relapsing course with poor control by traditional treatments.

Donors are selected among first relatives, age 18-70, excluding subjects with chronic, infectious or onco-haematological disease.

A multidisciplinary team, belonging to the FMT Transplantation Programme of OPBG, is involved: Digestive Endoscopy and Surgery Unit (selection of patients, visits and exams, endoscopy evaluation, FMT procedure), Human Microbiome and Parasitology Units (microbiota analysis and infectious screening for donor selection), and Immunology and Infectious Disease Unit (infectious surveillance before/after FMT, immunological studies).

A screening visit is performed for patients and donors, with the main purpose to exclude ongoing or past infections (optimization from European adult guidelines for paediatric recipients). In addition, the donor microbiota is assessed, in order to establish its quality and safety profile, and it is compared to the patient’s microbiota.

FMT procedure consists in the endoscopic instillation of faecal preparation from fresh stool, which may be released in the cecum (colonic disease) or in duodenum-jejunum (upper gastrointestinal disease).

Follow up visits are scheduled after 4-8-12 weeks, including blood tests and microbiota analysis. Endoscopic follow up is planned after 12 weeks.

Results: Two patients, affected by Ulcerative Colitis, were enrolled to the study, underwent FMT by colonoscopy, and completed the scheduled follow up. Patient 1 had a left sided colitis, in maintenance therapy with mesalamine. Follow up after FMT was uneventful and he reported absence of symptoms. Endoscopy revealed improvement of disease activity. Patient 2 had a pancolitis, in maintenance therapy with mesalamine and azathioprine. No complication occurred after FMT, and the patient reported clinical improvement with reduction of bowel movements. Follow up colonoscopy was similar to the baseline. A booster of FMT was done 16 weeks after the first one. The patient reported complete absence of symptoms (follow up ongoing).

Conclusion: The first Italian clinical trial on FMT in PIBD is ongoing. Two patients completed the study, without any complication. Both experienced a good clinical course, but the endoscopic evaluation after 12 weeks showed persistent disease activity. The pilot study will be completed with the enrolment of 10 subjects. Further steps include the design of a larger prospective trial for efficacy assessment and possible extension of FMT to medical conditions other than PIDS.

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**Objectives and Study:** Early onset IBD is an emerging form of paediatric IBD with distinct features in the pathogenesis and in the phenotype. The clinical pattern is often associated with isolated unclassified pancolitis, increased severity, aggressive progression and more resistance to many standard therapy. Thalidomide is shown to be effective and safe in treating refractory paediatric IBD. The aim of our study is to describe the experience of a single paediatric Gastroenterologic Centre in the use of thalidomide in the management of EOIBD.

**Method:** We carried out a retrospective review of EOIBD patients who received thalidomide in our Centre between January 2012 and November 2017. We analyzed clinical data, disease phenotype, medical history before treatment with thalidomide and at last follow-up.

**Results:** Six patients with EOIBD received thalidomide at our Centre in the considered period. Median age of onset of the disease was 2 years (range 0.5-4.5), 3 females and 3 males. All patients presented bloody diarrhea as main clinical feature with an active pancolitis, only one also having ileal disease. Five patients were diagnosed with unclassified IBD (IBD-U) presenting RCU-like features; the sixth one had a Crohn-like phenotype. All patients were dependant to high doses of steroids, refractory to thiopurines/methotrexate (2 patients) and refractory or intolerant to anti-Tumor Necrosis Factor (anti-TNF) agents (4 patients). The Crohn-like patient underwent urgent surgery (terminal ileum resection and ileostomy with colon diversion) with persistent steroid dependency. Genetic screening was negative for known genetic defects associated to EOIBD. The median disease duration before they started thalidomide was 9 months (range 2-36 months). All patients obtained steroid free clinical remission in about two months and maintained clinical and biochemical remission at a median follow-up of 0.8 years (range 0.2-5 years). Therapy was well tolerated. The only adverse event was asymptomatic peripheral neuropathy in three patients, that required dose reduction.

**Conclusion:** Patients with EOIBD have often an aggressive clinical course, frequently steroid dependant, with early need of immunosuppressors and surgical treatment. In our experience with steroid dependant severe EOIBD cases the use of thalidomide resulted in improve clinical remission and allowed steroid suspension, with a good tolerability and safety; the only adverse effect observed was the well known peripheral neuropathy. No risk of neoplastic diseases and severe infections related to thalidomide is described: this could be an important advantage to consider particularly in EOIBD, when the genetic screening to exclude primary immunodeficiency is still ongoing. In conclusion we suggest thalidomide in refractory and steroid dependant EOIBD patients as a good and safe option, at least before the use of the new biologics.

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Small-Intestinal bacterial overgrowth among children with inflammatory bowel disease

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Introduction: Small intestinal bacterial overgrowth (SIBO) is characterized by an abnormal bacterial proliferation in the small bowel. Crohn’s disease (CD) and ulcerative colitis (UC) share many common features with SIBO - diarrhea, bloating, weight loss, abdominal pain. SIBO has not been studied in children with inflammatory bowel disease (IBD).

Objectives: To assess the prevalence of SIBO among children with IBD and the relationship between SIBO and disease phenotype, localization and activity.

Methods: 43 children with IBD (29 CD and 14 UC) and 40 healthy controls were enrolled. 23 patients had active disease, whereas in 20 subjects the disease was in remission. SIBO was assessed using glucose hydrogen breath test (GHBT). Concentration of hydrogen was measured by LactoFAN analyser.

Results: 15 children with IBD (12 CD, 3 UC; 34.8%) and two control subjects (5%) were positive for GHBT. SIBO prevalence was significantly higher in IBD children as compared to controls (p<LT; 0.001). The occurrence of SIBO in CD (41.3%) was higher compared to UC group (21.4%) (p<LT; 0.05). Dysbiosis had a higher frequency among children with active disease (52.1%) compared to those in remission (15%) (p<LT; 0.05). There was no correlation of SIBO with the Pediatric Crohn’s Disease Activity Index in CD group. SIBO was significantly more frequent in CD children with stricturing pattern and ileum involvement.

Conclusions: SIBO is a frequent but underestimated condition in IBD, that might mimic acute flares. Stricturing phenotype in CD and active disease were associated with dysbiosis. SIBO diagnostic work-up followed by directed treatment is recommended in IBD children who present stricturing disease, especially in those with concurrent intestinal inflammation.

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Body composition, physical activity and quality of life in paediatric patients with inflammatory bowel disease

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Objectives and Study: Paediatric inflammatory bowel disease (IBD) is associated with malnutrition, weight loss and osteopenia which could result an altered body composition. IBD may cause abdominal pain, arthralgia and fatigue leading to impaired physical activity, affecting on muscle and bone strength. Our aim was to compare the body composition and physical activity in newly diagnosed patients with IBD receiving biologicals (anti-TNFα) and with normal population, and follow these parameters during a two month long period of time in the IBD population. According to our knowledge there is no other follow up study which investigates the body composition, physical activity and quality of life in children with IBD, and compares it to controls.

Method: Body composition (BC), Physical activity (PA) and Quality of Life (QoL) was detected in IBD patients (newly diagnosed IBD patients, (nIBD) n=18 and patients receiving anti-TNFα therapy (biological therapy (BT)) n=11). BC (fat mass index, (FMI) and fat free mass index (FFMI)) were measured by means of bioelectrical impedance. PA was assessed by Physical Activity Questionnaire (PAQ) and QoL by validated IMPACT-III questionnaire. The patients were measured at the beginning of the therapy (month 0, (M0)) and 2 month later (month 2 (M2)). BC and PA for controls were determined also (n=191, 10-18 years). Data were analysed with Mann Whitney U and Spearman correlation tests.

Results: During the investigated period PA improved significantly (p< 0.005) in the nIBD group but not in BT group. PA in nIBD group was significantly lower (p<0.0005) at M0 compared to controls, but there was no difference at M2. PA was lower in the BT group at M0 (p<0.0005) and M2 (p<0.005) compared to controls. During the investigated period FFMI increased with 3% in the nIBD and 1% in the BT group, while FMI increased with 2.3% in nIBD and decreased with 7% in BT group. There were no correlations between PA and FMI or FFMI in patients with IBD. QoL improved significantly in nIBD (p<LT; 0.005) but not in BT group. QoL in nIBD was significantly higher (p<LT; 0.05) at M2 compared to BT, but not at M0. In the control population, PA correlated negatively with FMI (p<LT; 0.05) in males and positively with FFMI (p<LT; 0.005) in females. The PA in younger population (10-14 years) were higher than in the older one (14-18 years, p<LT; 0.005).

Conclusion: Our data shows that the IBD patients have a lower PA compared to controls, however in the nIBD group PA improved significantly during the study period. The correlations in normal population between PA and BC were not detectable in our IBD population. Improved QoL was observed only in the nIBD but not in BT group. In conclusion, estimating PA can help in decoupling of various effects on body composition.
Impact of paediatric versus adult care setting on health care utilization in Dutch adolescents with inflammatory bowel disease

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Objectives and Study: Paediatric-onset inflammatory bowel disease (IBD) is different from adult-onset IBD with respect to disease severity and its effect on growth and development, and may require an age-appropriate treatment approach. We studied the effect of care setting (paediatric versus adult-oriented) on health care utilization in adolescent IBD patients.

Method: This is a Dutch population-based cohort study based on an insurance claims database covering 4.2 million insurees (approximately 25% of the Dutch population) from 2007 to 2014. We identified IBD patients aged 16 to 18 years and followed them until the age of 19 or transfer to adult care, whichever came first. We categorized patients according to care setting: paediatric versus adult-oriented. We defined outcomes as corticosteroid use, IBD-related hospital admission, IBD-related surgery, and biological use. We estimated Cox proportional hazards regression models to control for confounding by indication.

Results: Among 626 adolescent IBD patients, 380 (61%) were in paediatric and 246 (39%) in adult-oriented care. In paediatric care, patients were less likely to be treated with corticosteroids (hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.52-0.99) or biologicals (HR 0.57, 95% CI 0.34-0.97), and had fewer IBD-related hospital admissions (HR 0.58, 95% CI 0.37-0.92).

Conclusion: In a large and representative community cohort of Dutch adolescents with IBD, treatment in a paediatric care setting was associated with significantly lower steroid and biological use, without an increase in hospital admissions. Collaboration between paediatric and adult-oriented gastroenterologists in guideline development is warranted to achieve optimal care and outcomes in adolescents with IBD.

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Assessment of disease-specific knowledge of Polish children with inflammatory bowel disease

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Objectives and Aim: Patients' understanding of their disease processes correlates with better outcomes in many chronic relapsing and remitting illnesses such as inflammatory bowel disease (IBD). There is a limited data regarding patient's disease-related knowledge both among adults and children with IBD. The aim of the study was to assess IBD-related knowledge in a group of Polish IBD paediatric patients and their parents.

Methods: The study consisted of the two phases. In the first phase of the study Inflammatory Bowel Disease Knowledge Inventory Device (IBD-KID), which is a tool to measure an IBD-specific knowledge, was translated to Polish and validated. IBD-KID consists of 23 items exploring general knowledge of etiology, symptoms, complications, medications and side effects, surgery, psychosocial issues and research in IBD. In the second phase 12 months prospective multicenter study was conducted in four university-affiliated children's hospitals in Poland (cities of Warsaw, Cracow, Wroclaw and Olsztyn) in 2016. Only patients 10 years and older were eligible for the study. IBD was diagnosed according to Porto criteria. Children enrolled into study and their parents were asked to complete IBD-KID. Demographic and clinical data were also collected.

Results: 254 pairs child-parent participated in the survey answered the questionnaire. 55% of recruited patients were 15 years or older; males made 44.5%. Crohn disease was diagnosed in 164/254 (64.5%) of patients. Both parents and children presented high knowledge about the role of stress in exacerbating symptoms (correct answers given by 94.2% of parents and 87.4% of children) and the risk of transmitting IBD (correct answers provided by 94.1% of parents and 80.6% of children). There was a gap in knowledge about the role of surgical therapy in IBD (only 11.3% and 15.9% of correct answers to relevant items of questionnaire, respectively).

Parents had better IBD-related knowledge than children (p=0.002). There were no difference between patients with Crohn disease and ulcerative colitis (p=0.2). Greater parental knowledge was found to be correlated with a higher educational level (p=0.03) and membership of the Polish Association Supporting People with Inflammatory Bowel Disease (p=0.02). There were no association between sex (p=0.02), age of children (p=0.03), disease duration (p=0.9) and IBD-KID score.

Conclusions: There are gaps in knowledge about IBD among patients and their parents. The differences did not depend on the demographic and clinical characteristics of patients. The results of the study may be useful for planning of educational activities addressed to IBD patients and their families.
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-292

Efficacy of combination antibiotic therapy for refractory pediatric inflammatory bowel disease

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Objectives and Study: The pathogenesis of inflammatory bowel disease (IBD) is thought to involve an inappropriate and persistent inflammatory response to gut microbes in genetically susceptible individuals. Antibiotics have long been used in IBD with conflicting results. However, recent meta-analyses of randomized controlled trials documented a small but statistically significant benefit of antibiotics to induce remission in both CD and UC. Notably, Turner et al. demonstrated that treatment with combination oral antibiotics was effective in inducing remission for half of patients with refractory UC (1) in a small pediatric case series. Based on the above observations, we have used a similar regimen of antibiotics in patients with refractory IBD. Here, we report the first North American retrospective study describing the use of combination oral antibiotic therapy in pediatric IBD.

Method: We performed a single center retrospective study evaluating the efficacy of salvage therapy with a combination of at least 3 oral antibiotics for refractory colonic IBD in children. We included patients treated between November 1, 2014 and July 31, 2017 and excluded patients commenced on steroid therapy concurrently with the antibiotics. Disease activity was assessed by the Pediatric Ulcerative Colitis Activity Index (PUCAI) and CRP at baseline and subsequent time points. Need for surgery and escalation of therapy were assessed.

Results: Of the 51 enrolled patients, mean age was 14 ± 3.6 years and 26 (51%) were males. Twenty (39%) had colonic Crohn's disease (CD), 18 (35%) had UC and 13 (26%) had IBD-unclassified (IBDU). Mean disease duration was 3.3 ± 3.6 years. Twenty-seven (53%) patients were corticosteroid-dependent or resistant and 20 (40%) had failed 1 or more biologic. The most common antibiotic regimen was amoxicillin, metronidazole, and either doxycycline or ciprofloxacin, with vancomycin added for inpatient. Median duration of treatment (IQR) was 31 (25-65) days. All children had moderate to severe disease. Mean PUCAI at baseline was 50 and showed a mean decrease of 32 points at 4 weeks ± 1 week (p < 0.0001). Mean CRP at baseline was 19mg/L and also showed a statistically significant decrease at termination of antibiotics (8mg/L, p &LT; 0.003). Ten patients underwent surgical intervention by 1 year following antibiotic therapy.

Conclusion: The use of combination antibiotic as salvage therapy for refractory pediatric IBD may improve disease activity. Limitations of the study include small sample size and short follow-up interval in some subjects. Further trials to confirm efficacy of combination antibiotic in the pediatric population as salvage or bridge therapy is needed to confirm these results.

Reference:

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-293

Incidence of paediatric stricturing duodenal Crohn’s disease in South-East Scotland: a 12 year population-based cohort study

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Objectives and Study: Stricturing duodenal Crohn’s disease (CD) is a rare but serious presentation of CD causing significant morbidity. There are no data on its incidence rate in paediatric CD, and only estimates for adult CD. Our aim is to provide the first incidence data and case studies outlining this severe presentation in children.

Method: A regional cohort of prospectively acquired incident cases of PIBD diagnosed less than 16 years of age in paediatric services within a strict geographical area of South-East Scotland (based on postcode) was captured over a 12-year period (10.2005 - 09.2017). Incidence rates for all CD and for duodenal stricturing CD were calculated and standardised for age and sex with the Scottish Census of 2011. A retrospective review was conducted on the medical records of patients presenting with stricturing duodenal CD together with a detailed review of the available literature and consensus guidelines.

Results: In total 157 new cases of paediatric CD (&LT; 16yrs) were diagnosed within the study period. Median (IQR) age at diagnosis 13.1 (10.7-14.4) years; 64% male predominance. Overall CD incidence rate 5.80/100,000/year (95% CI 4.91-6.76) in South-East Scottish children, with a specific duodenal B2 phenotype disease incidence rate of 0.07/100,000/year (95% CI 0.01-0.27); representing 1.3% of incident cases at diagnosis. The two incident cases of stricturing duodenal CD (male aged 13.4yrs and female aged 15.5yrs) presented with typical systemic symptoms of weight loss, abdominal pain, anorexia and lethargy, together with recurrent vomiting suggestive of obstruction. Both cases partially responded to intensive and rapidly escalated medical therapy but eventually required surgery (laparoscopic gastroduodenostomy without resection). A detailed literature search confirmed there are no paediatric guidelines or case-reports relating to duodenal stricture as either a presentation or complication of CD.

Conclusion: Duodenal stricture is a rare but serious presentation of CD causing significant morbidity and not currently covered in the paediatric literature or consensus guidelines. Best practice medical and surgical management remain uncertain and require further research.

Disclosure of interest: David Wilson has received consultancy fees, lecture fees or support to attend meetings by AbbVie, Takeda and Falk.

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Patterns of mucosal inflammation in paediatric inflammatory bowel disease: Striking overexpression of IL-17A in children with ulcerative colitis

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1Children’s Hospital, Mainz, Germany
2Institute of Medical Biostatistics, Epidemiology and Informatics, Mainz, Germany

Objectives and Study: With over two million people afflicted, inflammatory bowel disease (IBD) is a relevant cause for morbidity in Europe. Approximately 25% of patients with IBD are diagnosed during childhood or adolescence, which is often associated with a high degree of physiological and psychological suffering. However, therapeutic options remain unsatisfying in many cases. An aberrant immune response is thought to be a crucial factor in the pathogenesis of IBD. While immunological patterns are fairly well described in adults with IBD, the knowledge in paediatric patients is scarce. Thus, it was the aim of our study to characterize immunological patterns within the intestinal mucosa of children with Ulcerative Colitis (UC) and Crohn’s Disease (CD), thereby identifying potential therapeutic targets.

Method: Fifteen children with UC (mean age: 13.73 ±2.6 years), twelve children with CD (mean age: 13.42 ±2.64 years) and twenty-five children with no evidence of inflammatory bowel disease (mean age: 12.08 ±4.07 years) were included in the present study. During diagnostic colonoscopy intestinal tissue biopsies were taken and preserved for analysis of immunological markers. Relative expression of signalling molecules (TNF, IFNγ, IL-6, IL-9, IL-12A, IL-12B, IL-23A, IL-17A, IL-22, IL-10, TGFβ1, SMAD7) and transcription factors (T-bet, GATA3, PU.1, RORγt, FOXP3) associated with different T helper cells (T_{h}) and regulatory T cells (T_{reg}) were determined by quantitative polymerase chain reaction. Additionally, clinical data were collected from medical records.

Results: Strikingly, IL-17A was vigorously expressed in UC patients compared to both non-IBD patients (p &LT; 0.001; fold change 71) and CD patients (p &LT; 0.001; fold change 6). IL-22 was strongly increased in UC patients only (p &LT; 0.001; fold change 17). Expression of typical proinflammatory cytokines (TNF, IFNγ, IL-6) was pronounced in IBD patients with fold changes being more prominent for CD. T_{reg} associated cytokines (IL-10, TGFβ1) were also increased especially in CD patients, although to a lower extent.

Conclusion: Our findings emphasize the complex involvement of different subtypes of T helper cells as well as regulatory T cells within the pathogenesis of IBD. The outstanding overexpression of IL-17A which can be found in children with UC and the high expression of IL-22 in the same group suggest an important role of T_{h}17-associated cytokines in paediatric UC, which might be a subject for further investigation in search of a target for therapeutic intervention. Additionally, IL-17A could be a useful marker for differentiation of paediatric CD and UC in the pathway of clinical examination. Upregulation of proinflammatory cytokines compared to immunoregulatory cytokines especially in CD patients furthermore indicates a lack of mucosal immunological homeostasis being a key problem.

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Gastroenterology - Inflammatory bowel disease

G-P-295

Faecal calprotectin in paediatric juvenile polyps versus inflammatory bowel disease

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Objectives and Study: Faecal calprotectin (FC), a stool biomarker of bowel inflammation is increasingly used as part of the non-invasive investigations of gastrointestinal symptoms in children. Elevated FC levels are often seen in inflammatory bowel disease (IBD), but some studies have also reported elevated FC amongst children with juvenile polyps (JP). The aim of the study was to investigate the use of FC in the diagnosis of JP and to compare the average calprotectin levels amongst children with JP and those with IBD.

Method: We collected data retrospectively of patients aged ≤18 years diagnosed with JP and those diagnosed with IBD with available FC levels in our centre over a 5 years' period (2011-2016). FC levels were obtained from electronic biochemistry records and hospital clinic letters. The comparison of FC levels between children with JP vs. IBD was limited to those with a calprotectin result within 3 months (90 days) of the diagnostic biopsy. Possible demographic confounders (age) were investigated.

Results: 26 cases of JP were identified between 2011-2016 in our centre. 14/26 (54%) had a FC result available, of which 13/14 were within 3 months of the date of the diagnostic biopsy for JP. In the comparison group (IBD) we identified 33 children with biopsy diagnosis of IBD and a calprotectin result within 3 months of the biopsy. All children (JP and IBD) had calprotectin levels above 'normal' (60 µg/g). Average calprotectin levels seemed to be higher amongst children with IBD than those with juvenile polyps, although this did not reach statistical significance (p=0.07). Interestingly, the children diagnosed with IBD were on average significantly older (mean 12.0 years, SD 3.5) than those with juvenile polyps (mean 5.5 years, SD 4.1) (p< 0.001).

<table>
<thead>
<tr>
<th>Calprotectin (µg/g)</th>
<th>IBD (n=33)</th>
<th>Juvenile polyps (n=13)</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>1175 (1214)</td>
<td>625 (690)</td>
<td>P=0.06 (T-test)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>872 (408-1352)</td>
<td>330 (230-662)</td>
<td>P=0.07 (Wilcoxon)</td>
</tr>
</tbody>
</table>

[Calprotectin values in juvenile polyps vs. IBD]

Conclusion: Calprotectin levels were available for about half of cases of JP, and were on average elevated, although perhaps to a lesser extent than in children with IBD. There is also potential confounding by age, as children with JP were on average significantly younger than those with IBD. However, as other studies suggest that younger children have higher average calprotectin, it may be that the true difference in calprotectin levels between the groups is actually under-estimated in this study. The differentiation between IBD and JP, as well as other inflammatory conditions of the colon and/or small intestine, cannot be based solely on FC. The high FC found in these non-IBD conditions may be one of the reasons for the low specificity of FC as compared to its sensitivity.

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Phenotypic and genotypic characterization of inflammatory bowel disease in children under six years of age in China

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¹Children's Hospital of Zhejiang University, Hangzhou, China

Objectives: The aim of this study was to analyze the clinical differences between monogenetic and non-monogenetic very early onset inflammatory bowel disease (VEO-IBD) and to investigate the phenotypic and genotypic characterization of monogenetic IBD through genetic testing.

Methods: A retrospective analysis was performed in children aged 0 to 6 years diagnosed with VEO-IBD in a tertiary hospital in southern China from 2005 to 2017. Clinical data of VEO-IBD patients were collected, and the genetic characteristics were analyzed using whole exome sequencing (WES) and target gene panel sequencing (TGPS).

Results: A total of 54 VEO-IBD patients, including 57.41% of patients with disease onset before the age of two years, were included in this study. The ratio of male to female was 2.18:1. While the diagnosis of CD or CD-like intestinal manifestations accounted for 72.22% of VEO-IBD cases, UC or UC-like intestinal manifestations and IBD-U accounted for 9.26% and 20.37% of cases, respectively. Nine patients (16.67%) were identified to have monogenetic IBD by genetic testing according to their clinical presentation. The median age of disease onset in the monogenetic group was less than that of the non-monogenetic IBD group with 1 M (0, 72 M), 19.5 M (0, 72 M), respectively, \( p = 0.008 \). And the median age of disease diagnosis in monogenetic group were less than that of non-monogenetic IBD group with 18 M (IQR: 4 to 78) and 43.5 M (IQR: 3 to 173), respectively, \( p = 0.021 \). The incidence of perianal disease in the monogenetic group was higher than that of the non-monogenetic group \( (p=0.001) \). There were no significant differences between the Z-scores of weight for age and height for age between the two groups. Laboratory findings demonstrated similar results in the two groups. Next generation sequencing was performed in 16 patients. Five patients were observed to have IL 10 receptor deficiency, two patients had chronic granulomatous disease (CGD), one patient had common variable immunodeficiency disease (CVID) and one patient had XIAP deficiency.

Conclusions: There was a high proportion of monogenetic IBD in the VEO-IBD group. Monogenetic IBD and non-monogenetic IBD showed similar clinical features. Furthermore, next generation sequencing played an important role in the diagnosis of VEO-IBD patients with high risks of monogenetic IBD.

<table>
<thead>
<tr>
<th></th>
<th>Monogenetic IBD</th>
<th>None-monogenetic IBD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/1</td>
<td>28/17</td>
<td></td>
</tr>
<tr>
<td>Median age of disease</td>
<td>1 (0, 72)</td>
<td>19.5 (0, 72)</td>
<td>0.008*</td>
</tr>
<tr>
<td>onset (M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age of disease</td>
<td>18 (4, 78)</td>
<td>43.5 (3, 173)</td>
<td>0.021*</td>
</tr>
<tr>
<td>diagnosis (M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration before</td>
<td>6 (2, 29)</td>
<td>9 (0, 104)</td>
<td>0.668</td>
</tr>
<tr>
<td>diagnosis (M)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[The general data of VEO-IBD patients]

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Comparison of clinical phenotypes between different ages of disease onset: A twelve-year experience with pediatric inflammatory bowel disease at a single center in southern China

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¹Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Objectives and Study: The objective of this single-center study was to compare the clinical phenotypes of different groups based on the age of disease onset in southern China.

Method: A retrospective analysis of children 0 to 18 years of age diagnosed with IBD was performed at a tertiary hospital in south China from 2005 to 2017. Patients' data were compared between infantile onset IBD (IO-IBD), very early onset IBD (VEO-IBD), early onset IBD (EO-IBD) and late onset IBD (LO-IBD).

Results: Of the 127 IBD patients identified during the 12-year study period, 105 patients (82.68%) were diagnosed with CD, and CD was the predominant diagnosis in each group. No positive family history was found in our study. Symptoms of diarrhea, bloody stools and growth failure in IO-IBD group were significantly more common compared with other groups (p=0.001, p=0.000 and p=0.004, respectively). Perianal disease complications in IO-IBD occurred more than in other groups (p=0.024). The predominant disease location in IO-CD was colonic involvement (73.33%). And patients older than six years of age primarily presented with both colonic and small bowel disease (54.17%). VEO-IBD patients need higher rate of immunosuppressant (68.18%) and infliximab (50%). The abdominal surgery in the VEO-IBD group was the highest (P=0.029).

Conclusions: Pediatric IBD patients have dramatically increased in the past ten years, and CD was the predominant diagnosis in the four groups. IO-IBD and VEO-IBD exhibit a unique clinical phenotype, and VEO-IBD showed more severe clinical course in our study.

<table>
<thead>
<tr>
<th></th>
<th>IO-IBD</th>
<th>VEO-IBD</th>
<th>EO-IBD</th>
<th>LO-IBD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>23 (18.1)</td>
<td>22 (17.3)</td>
<td>18 (14.2)</td>
<td>64 (50.4)</td>
<td></td>
</tr>
<tr>
<td>Gender (M / F)</td>
<td>15/8</td>
<td>13/9</td>
<td>10/8</td>
<td>38/26</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>15 (65.2)</td>
<td>18 (81.8)</td>
<td>15 (83.3)</td>
<td>57 (89.1)</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>1 (4.3)</td>
<td>3 (13.6)</td>
<td>3 (16.7)</td>
<td>2 (3.1)</td>
<td></td>
</tr>
<tr>
<td>IBDU</td>
<td>7 (30.4)</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td>5 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Median age of disease onset, M (range)</td>
<td>4.0 (0-13)</td>
<td>55.5 (29-72)</td>
<td>103 (83-119)</td>
<td>149.5 (121-183)</td>
<td></td>
</tr>
<tr>
<td>Median age of disease diagnosis, M (range)</td>
<td>19 (3-116)</td>
<td>65.5 (33-173)</td>
<td>114 (84-134)</td>
<td>157 (123-199)</td>
<td></td>
</tr>
<tr>
<td>Median time before diagnosis, M (range)</td>
<td>9 (1-104)</td>
<td>9.5 (0.4-101)</td>
<td>5 (1-24)</td>
<td>5 (1-48)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

[Comparison of IBD patients with different age of diagnosis]

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Steroid treatment for longer than two weeks leading to admission predicts higher colectomy rates in ulcerative colitis

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²University of Liverpool, Liverpool, United Kingdom
³Royal Liverpool and Broadgreen University Hospital NHS Trust, Liverpool, United Kingdom

Objectives and Study: The value of second-line treatment and rescue therapy in acute severe colitis (ASC) has been established. There is lack of evidence to which factors determine adverse outcome in children with ulcerative colitis over time. Our aim was to identify risk factors for colectomy in children admitted for flare-up of ulcerative colitis.

Method: We conducted a systematic retrospective case note review in our major tertiary GHN service and identified n=32 patients admitted for medical treatment of active ulcerative colitis. We divided patients into 2 cohorts: Group A (n = 10); received steroids >2 weeks before admission, and Group B (n = 22); received steroids < 2 weeks before admission or did not receive steroids prior to admission. We compared both groups regarding PUCAI scores, proportion of clinical remission, flare-up, colectomy, and co-medication (azathioprine/6-mercaptopurine, infliximab) after 1, 3 and 5 years of admission. Data were analysed using Fisher's exact test.

Results: The colectomy rate was significantly higher in Group A (received steroids >2 weeks) after 1, 3 and 5 years (Table 1). Patients in Group B were significantly higher on azathioprine treatment. Group B had a higher proportion of initial flare-up as acute severe colitis. Notably, both groups did not differ between median PUCAI score on all admissions, IV-steroid dosage (high or low dose protocol), infliximab treatment, or antibiotics given at first flare-up.

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n = 32)</th>
<th>Group A (n = 10); received steroids &gt;2 weeks before ASC admission</th>
<th>Group B (n = 22); received steroids &lt;2 weeks before ASC admission or did not receive steroids</th>
<th>Fisher's test (P-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare up rate at 5 years, n (%)</td>
<td>13 (40.6%)</td>
<td>2 (20.0%)</td>
<td>11 (31.8%)</td>
<td>0.050*</td>
</tr>
<tr>
<td>Azathioprine/6MP rates at 1 year, n (%)</td>
<td>27 (84.4%)</td>
<td>7 (70.0%)</td>
<td>20 (90.9%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Azathioprine/6MP rates at 5 year, n (%)</td>
<td>20 (62.5%)</td>
<td>3 (30.0%)</td>
<td>17 (77.3%)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Infliximab rates at 1 year, n (%)</td>
<td>2 (6.3%)</td>
<td>1 (10.0%)</td>
<td>1 (4.5%)</td>
<td>0.534</td>
</tr>
<tr>
<td>Colectomy at 1 year, n (%)</td>
<td>3 (9.4%)</td>
<td>3 (30.0%)</td>
<td>0 (0%)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Colectomy at 3 years, n (%)</td>
<td>4 (12.5%)</td>
<td>4 (40.0%)</td>
<td>0 (0%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Colectomy at 5 years, n (%)</td>
<td>5 (15.6%)</td>
<td>5 (50.0%)</td>
<td>0 (0%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Median PUCAI score</td>
<td>55 (43.8-65)</td>
<td>42.5 (40-56.3)</td>
<td>50 (45-55)</td>
<td>0.241</td>
</tr>
<tr>
<td>Antibiotics at first flare up, n (%)</td>
<td>17 (53.1%)</td>
<td>4 (40.0%)</td>
<td>13 (59.1%)</td>
<td>0.450</td>
</tr>
</tbody>
</table>
Conclusion: Patients receiving steroids for longer than 2 weeks are at greater risk to requiring colectomy after 1, 3 and 5 years than patients admitted earlier. This effect was irrespective to the cumulative IV-steroid dosage, use of infliximab, or IV antibiotics, or initial flare-up as acute severe colitis. Azathioprine may provide protection against colectomy.

Our study indicates the need to consider earlier escalation treatment for children not responding within two weeks of oral corticosteroids.

Disclosure of interest: Dr Marcus KH Auth had received travel grants or consultation fees from AbbVie, Nutricia, MSD, Dr Falk

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Methotrexate as maintenance therapy for paediatric Crohn's Disease a single centre study

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Objectives and Study: Methotrexate is a recommended treatment option for maintaining steroid free remission in children with Crohn's Disease (CD). It is useful in children who are intolerant or unresponsive to thiopurines.

Aim: To evaluate the use of methotrexate for maintenance of remission in children with CD from our unit.

Method: A retrospective analysis of the electronic records of all children prescribed methotrexate for Inflammatory Bowel Disease (IBD) over a 7 year period was carried out. Information was obtained on the age at diagnosis, age at initiation of methotrexate and duration. Information on side effects experienced, combination therapy with anti TNF and indications for discontinuing therapy was also obtained.

Results: Of a total of 322 children with IBD, 49 were evaluated for maintenance therapy with methotrexate. Due to severe needle phobia in one child, and resolution of symptoms in the other treatment was withheld. All children received ondansetron and folic acid, and received regular blood monitoring. The dose was reduced in some patients when established on treatment and in remission.45 children with a diagnosis of CD and 2 children with a diagnosis of Inflammatory Bowel Disease Unclassified (IBDU) received methotrexate for a duration of between 2 weeks and 64 months. There were 32 male (68%) and 15 female (32%). Age range at initiation - 4 years 8 months-16 years 8 months (median 12 years). Only 2 children were thiopurine naïve at the time of commencement of methotrexate. All but 2 children were initially commenced on subcutaneous route of administration; of which 14 (30%) where switched to the oral route to improve compliance. Methotrexate monotherapy was successfully established in 23 (49%) - median duration of use 12 months, but discontinued in 4 patients due to side effects. Of the 24 patients who received methotrexate as combination therapy with anti - TNF in 50% methotrexate was discontinued (duration of use 2 weeks -64 months); and thiopurine recommenced in 75% of these. Side effects reported include leg cramp, paraesthesia, nausea and vomiting and labile mood.
Conclusion: Methotrexate is well tolerated in children requiring maintenance therapy for CD. Symptoms of vomiting and nausea may be ameliorated by switching route of administration, reducing the dose and ensuring compliance with antiemetic therapy and folic acid. Approximately 50% of children will require methotrexate in combination with anti-TNF therapy.

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Partial enteral nutrition improves growth in pediatric Crohn's disease

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²Technical University of Munich, Freising, Germany  
³Children's Hospital Munich-Schwabing, Technical University, Munich, Germany

Objectives and Study: Exclusive enteral nutrition induces remission and improves growth in pediatric Crohn's disease. We investigated short- and long-term efficacy of partial enteral nutrition (PEN) therapy on height development, lean and fat body mass, microbiome composition and clinical course of pediatric Crohn's disease (CD) patients.

Methods: We performed a two center, non-randomized controlled intervention study in CD patients aged ≤T; 18 years who were in remission or had mild disease activity at inclusion. Intervention group received a casein based complete liquid formula (Modulen® IBD), providing ~25% of daily calories. Control group did not receive nutritional intervention. Both groups continued their medical maintenance treatment. Patients were evaluated at baseline and after 3, 6, 9 and 12 months. We collected data on disease activity (weighted Pediatric CD activity index, wPCDAI), anthropometry, lean and fat body mass by air displacement plethysmography and laboratory indices, as well as fecal samples to determine microbiota composition by 16S rRNA gene sequencing. Basic characteristics between the two groups were analyzed with unpaired t-tests, while paired t-tests were applied for comparisons between different time points. Here we report the 6 months outcome data. Significance level was p< 0.05.

Results: Of 42 CD patients recruited between 01/2016 and 07/2017, 22 patients agreed to Intervention (PEN) (mean age at diagnosis 11.8 ± 2.9 years, 55% male), and 20 to serve as controls (c) (mean age at diagnosis 9.0 ± 3.7 years, 55% male). The groups were comparable regarding disease location (Paris classification), baseline disease activity (wPCDAI≤L; 12.5 indicating remission: PEN 20/22 and controls 18/20) and maintenance treatment (anti-TNF: PEN 13/22 and controls 14/20), but PEN patients were older at time of study inclusion (mean (PEN) = 15.0 ± 1.9 years; mean(c) = 13.1 ±3.3 years, p=0.04). Between baseline and month 6, there was a significant increase in z-scores for height in the PEN group (p=0.02), but not in the controls (p=0.12). Inflammatory markers (CrP, ESR and fecal calprotectin) and wPCDAI did not differ between groups during follow up. Total relapse rate was low 6/42 (PEN 3/22, control 3/20, ns). No changes in z-scores for weight, or lean or fat body mass occurred over time in both groups. PEN was not associated with changes in fecal microbiota composition (beta diversity) compared to controls.

Conclusion: In our cohort of pediatric CD patients in remission, PEN providing 25% of daily calories seems to improve growth without significant changes in lean and fat body mass or fecal microbiota composition.

Disclosure of interest: This study was supported by research grants from the European Crohn's and Colitis Organization (ECCO), (ECCO-Nestlé Health Science Nutrition Fellowship 2015) and the Faculty of Medicine of the Ludwig Maximilian's University (LMU), support programme „Förderprogramm für Forschung und Lehre (FoFoLE)“, Grant No 968.

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Frequency and characteristics of gastric involvement in children with ulcerative colitis

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Objectives: Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that typically affects the colonic mucosa. However signs of gastric inflammation have been reported in up to 40% of patients with UC and may pose a dilemma in the differential diagnosis with Crohn's disease (CD). We aimed at evaluating the prevalence of gastric inflammation and at describing its features in a population of children with active UC in comparison with children with active CD.

Methods: We performed a retrospective study identifying patients with a diagnosis of CD and UC based on the Porto criteria within the electronic database of the Gastroenterology Unit of the IRCCS Burlo Garofolo, in Trieste, Italy, from January 2000 to August 2017. Demographical (sex, age at diagnosis), clinical (IBD type, disease localization according to the Paris classification, associated hepatobiliary disease, presence of symptoms of gastric involvement and ongoing therapies), endoscopic and histological data at diagnosis were collected. Data of patients with UC were matched with children with CD. Finally, the features of patients with UC with and without gastritis were compared.

Continuous variable were reported as mean and standard deviations while categorical variables were summarized by frequencies. Comparisons were performed with t-test and with the Fisher exact test; values < 0.05 were considered significant.

Results: Two hundred ninety four patients were identified: 136 (46%) had CD and 158 (54%) had UC. EGDS reports were available for 102/136 (75%) children with CD and for 44/157 (28%) patients with UC; endoscopic pathological findings were reported in 78 (76%) and 24 (54%), respectively (p < 0.01).

Fourteen patients with UC and gastritis and 28 patients with CD and gastritis were female. The mean age at gastritis diagnosis was 14.1 ± 3.4 years for UC and 13.3 ± 3.9 years for CD. For patients with CD and gastritis localization of intestinal disease was as follows: 11 (14%) ileum, 12 (15%) colon and 55 (71%) ileo-colon; among patients with UC and gastritis 17 (70%) had pancolitis. Eleven (52%) patients with UC and 28 (36%) patients with CD and endoscopic gastritis reported gastric symptoms. Hyperemia of the gastric mucosa was found in 39 (38%) patients with CD and in 13 (30%) with UC; aftae or ulcers were reported in 37 (36%) patients with CD and in 7 (16%) patients with UC. None of the latter had deep or linear ulcers. Associated duodenal lesions were found in 39 (39%) patients with CD and in none with UC (p < 0.01). Histological features of the specimens from patients with endoscopic gastritis was reported as “typical for CD” in 10 patients while in the remainder and in all patients with UC was defined as unspecific inflammation. No statistically significant differences were found comparing the demographic and the clinical characteristics of UC patients with and without gastritis.

Conclusions: Gastric inflammation is frequently found in patients with UC and is generally symptomatic but endoscopic and histological findings are non specific for inflammatory bowel disease. Contrary to patients with CD none of the patients with UC with gastritis had signs of duodenal involvement. No specific clinical feature was found to differ between patients with UC and gastritis and patients with UC without gastritis.

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-302

Serum infliximab concentration by point-of-care devices in paediatric inflammatory bowel diseases

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Objectives and Study: Anti-tumor necrosis factor (TNF) agents, in particular infliximab (IFX), have become the mainstay of treatment in refractory inflammatory bowel diseases (IBD), also in paediatric patients. Furthermore, they also seem to be promising as first line treatment in early-stage IBD, yet their widespread use in all patients could not be affordable by the national health systems. Therapeutic Drug Monitoring (TDM) is an effective strategy in the management of IBD patients and is widely used in the adjustment of the originator infliximab therapy. Two validated point-of-care devices for IFX (POC IFX) quantification are already available in the market. The aim of this study was to compare the point-of-care IFX devices for quantification of IFX by comparing it with two validated ELISA assays.

Method: We studied 33 samples from 20 paediatric IBD patient (median age 15.46, interquartile range 13.55-16.90) (Crohn’s disease 16; ulcerative colitis 4) from the Paediatric Gastroenterology of Trieste, treated with a standard maintenance therapeutic scheme. Serum samples were collected consecutively over one year period, before infusion. Infliximab was measured using two commercial ELISA assays, one, Lisa-tracker, used as reference at the certified laboratory in Udine Hospital, the other, Promonitor, tested as a comparison ELISA at Trieste Children's Hospital, and two POC IFX assays, Quantum Blue (POC IFX/QB) and Rida-quick (POC IFX/RQ) at Trieste Children's Hospital. Intraclass Correlation Coefficient (ICC) was assessed for quantitative comparison and weighted kappa (95% CI) statistics were used for qualitative analysis.

Results: Quantitative comparison showed an excellent ICC between POC IFX assays and the two ELISA-based established methods. ICC was 0.82 and 0.87 for POC IFX/Quantum blue and POC IFX/Rida-quick with the reference ELISA assay, respectively, and 0.87 for the two ELISA assays. For qualitative comparison, weighted kappa (95% CI) statistics were determined after stratification of results by therapeutic interval (< 3 ug/mL, 3-7 ug/mL and >7 ug/mL). A good agreement was shown between pairs of assays, with kappa of 0.67 and 0.80 for POC IFX/QB and POC IFX/RQ respectively with reference ELISA and 0.81 between the reference and comparison ELISAs.

Conclusion: POC IFX assay, a methodology already validated and available in the market to assess IFX concentration in adult patients, showed good agreement with both ELISA-based established assays when used in paediatric patients. This new methodology, that delivers results in 15 min, could be implemented as a tool in TDM of IFX in children with IBD.

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Objectives and study: Psychosocial and functional outcomes after intestinal resection in pediatric Crohn's disease (CD) are lacking. Therefore, we assessed (I) health-related quality of life (HRQOL) and colorectal function, (II) surgical outcomes associated with colorectal function, and (III) satisfaction with surgery, after ileocecal resection for pediatric CD.

Method: A multi-center cross-sectional study was conducted in CD patients that underwent ileocecal resection during childhood. HRQOL was assessed using the SF-36 (in patients ≥18y at follow-up) compared to HRQOL in the general population. Scores were aggregated into two summary measures: Physical and Mental Component Summary. Colorectal function was assessed using COREFO compared to colorectal function in a normal function cohort. The COREFO assesses a total score based on five categories: incontinence, social impact, stool frequency, stool-related aspects (pain during bowel movements, blood loss, and local skin problems), and use of medication to thicken bowel movements. Associations between COREFO total or category scores, and patient characteristics were analyzed using multivariate linear regression (corrected for sex and age at follow-up). Satisfaction was scored on a 5-point Likert scale.

Results: Eighty patients (50% male, median age 23.0 years) were included. Physical HRQOL in patients was impaired (SF-36[mean]: CD: 47 vs. general: 54, p&LT; 0.001), while mental HRQOL was similar compared to the general population. Overall colorectal function was impaired in CD patients compared to a cohort with normal colorectal function (COREFO[mean]: CD: 12.6 vs. normal: 7.2, p&LT; 0.001). Higher clinical disease activity was associated with higher COREFO total score (B: 0.27 [95%CI: 0.16-0.39], p&LT; 0.001), and all category scores. A longer duration since primary ileocecal resection was associated with a higher COREFO total score (B: 0.40 [95%CI: 0.05-0.75], p=0.025), and a higher defecation frequency category score. A severe complication after ileocecal resection was associated with a higher frequency category score, and recurrent abdominal surgery with a higher need of medication category score. Satisfaction with surgery was as follows: 81% satisfied or very satisfied, 11% neither satisfied nor dissatisfied, 8% dissatisfied or very dissatisfied.

Conclusion: Physical HRQOL and colorectal function are impaired in CD patients who underwent ileocecal resection during childhood. Higher clinical disease activity and adverse surgical outcomes are associated with impair colorectal function. This emphasizes the need for careful post-operative monitoring and prophylactic therapies in pediatric CD patients.
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-304

(1→3)-β-D-Glucan levels correlate with calprotectin levels in pediatric Crohn’s disease: A cohort study

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Objectives and Study: (1-3)-β-D-Glucan (BDG), a component of most fungal cell walls, might be a useful indicator of gut inflammation. The objective of this study was to evaluate whether higher serum BDG levels are correlated with inflammation in pediatric Crohn’s disease.

Method: All patients under the age of 18 years followed for Crohn’s disease at a French university hospital between December 2013 and December 2015 were included. Fifty-nine BDG (Fungitell®, Cape Cod) assays were performed in forty-five patients with a mean age of 13.3±6.6 years.

Results: A positive correlation was demonstrated between serum BDG levels and fecal calprotectin levels (r = 0.35, p = 0.02). Conversely, no correlation was observed between serum BDG levels, C-Reactive Protein and Erythrocyte Sedimentation Rate or Weighted Pediatric Crohn’s Disease Activity Index.

Conclusion: This study therefore shows that serum BDG levels may constitute an additional marker for the evaluation of gastrointestinal inflammation in children with Crohn’s disease. However, this result needs to be confirmed by further studies.

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The importance of mean platelet volume in childhood inflammatory bowel disease

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Objectives and Study: The aim of the study is to evaluate the mean platelet volume (MPV) levels in the inflammatory bowel disease (IBD) in childhood and adolescence and to determine whether platelet volume is a useful marker in predicting the activation of the disease.

Method: The study group included 26 IBD patients (consisting of 18 ulcerative colitis (UC), 6 Crohn’s disease (CD), and 2 indeterminate colitis patients) followed-up at Dr. Behçet Uz Children's Hospital, Paediatric Gastroenterology, Hepatology and Nutrition Department between August 2004 and October 2016. The data of these patients were screened retrospectively and the demographic, clinical and laboratory characteristics were evaluated. The changes in MPV during the activation, remission and relapse periods of the disease and correlation with other disease activity markers were investigated.

Results: The study group consisted 26 IBD patients (F/M: 11/15) and 71 healty controls. The mean age of the patients at diagnosis was 14.2±2.8 years. The most common symptoms were bloody diarrhea, weight loss and abdominal pain. We used the Paediatric Ulcerative Colitis Activity Index (PUCAI) for UC and the Paediatric Crohn Disease Activity Index (PCAI) for CD to determine disease activity. In terms of hematologic parameters, the IBD group had statistically significantly higher leukocyte count and lower hemoglobin values compared with the control group (p<0.05). Mean platelet count was significantly higher (p<0.05) and MPV was significantly lower (p<0.05) in the IBD group. A significant negative relationship was obtained between mean platelet count and MPV. There was no significant difference between MPV values in the activation, remission and relapse periods (p>0.05). The mean platelet count and MPV values were not correlated significantly with both the C-reactive protein level and erythrocyte sedimentation rate (p>0.05).

Conclusion: We suggest that MPV is a simple and inexpensive method that can be useful in the diagnosis of IBD but does not provide significant results to determine the disease activity.
Early Onset Inflammatory Bowel Disease in the UK Southwest population

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Objectives and Study: To characterise epidemiology, phenotype and clinical outcome of children with Early Onset Inflammatory Bowel Disease (EO-IBD) diagnosed aged < 10 years, and compare data between two age groups: 2-5 years and 6-9 years.

Method: Baseline demographics, diagnostic investigations, and phenotype at diagnosis was collected for all children diagnosed between May 2004 and June 2017. Treatments, clinical and surgical outcomes were analysed at 1, 2, 5 and 10 years follow up. This was a retrospective review of prospective data.

Results: During the period of this study, there were 664 new IBD cases, with an average of 42 new cases per year up to 2010 and 60 since then (rs=0.57; p=0.03). 136 children (57% Male) with EO-IBD were identified (20% of total IBD cases; 10 new cases per year on average, throughout the entire period - rs=0.08; p=0.78); 64 children (64% Male) had Crohn's disease - CD, 45 (47% Male) Ulcerative Colitis - UC and 27 (56% Male) IBD-Unclassified - IBDU. 32 children were aged 2-5 years (37.5% CD, 40.6% UC, 21.9% IBDU) and 104 children (50% CD, 30.8% UC, 19.2% IBDU) aged 6-9 years.

Children aged 2-5 years at diagnosis had greatest time from symptom onset to diagnosis (mean 13 months vs 8 months, p=0.37); positive family history (61% vs 45%, p=0.26); compared to the older age group. Bloody diarrhoea, extra gastrointestinal manifestations and anaemia were markedly higher in younger children (70%, 72%, 83% vs 58%, 57%, 57%, p=0.20, p=0.13, p=0.17, respectively).

Children with EO-CD predominantly had nonstricturing and nonpenetrating (93%) disease. Those aged 2-5 years with CD were more likely to have ileal sparing (67% vs 29%, p=0.02) and less likely to have peri-anal disease (42% vs 59%, p=0.28) than the older group. Use of exclusive liquid diet was lower in the younger group (27% vs 65%, p=0.04), 5-ASA use was common in both age groups (36% vs 29%, p=0.72). Anti-TNF was used in 10% of cases in the first year and 37% during follow up. Surgery during follow up was more common in the older patients (17% vs 83%, p=0.99).

In UC cases, 79% presented with pancolitis (82% aged 2-5 years, 78% aged 6-9 years, p=0.69) and none had rectal sparing. Severe disease was seen more commonly in the younger patients (36% vs 19%, p=0.43). 5-ASA use was common in both age groups (83% vs 94%, p=0.31) as was steroid use (67% vs 87%, p=0.19) during the first year. Anti-TNF was used in 9% of cases in the first year and 22% during follow up. Surgery during follow up was more common in the younger patients (71% vs 29%, p=0.01).

In the IBDU group, ileal sparing was seen in 81.5% and there were no surgical cases. The initial diagnosis was changed during follow up in 9 of these patients (6 to CD and 3 to UC) and 3 other patients were reclassified as IBDU (1 initially CD and 2 UC).

Conclusion: Although the incidence of IBD overall is increasing, the incidence in EO-IBD appears to be static. Male preponderance in the cohort overall and dominance of UC and higher rates of positive family history in the younger group are consistent with previous studies. The delay in diagnosis for younger children is of concern and may explain the higher rates of anaemia at diagnosis.

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First use of ustekinumab in treatment of paediatric Crohn disease, in Portugal

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Objectives and Study: The aim of this report was to describe the first case of paediatric inflammatory bowel disease patient treated with ustekinumab, in Portugal.

Method: Hospital’s electronic records of the children treated with ustekinumab, in a Paediatric Gastroenterology Unit, in a tertiary Hospital.

Results: Female 15 years old adolescent, who was diagnosed as fistulising Crohn disease at age twelve. At this age, she presented with 33.3% height loss during last two years, perianal fistula and large inflamed perianal skin tags. Esophagogastroduodenoscopy was normal and ileocolonoscopy shown ileitis and ileal aphthous ulcers. Magnetic resonance enterography confirmed ileal oedema. Azathioprine (AZA) and prednisolone therapy were instituted because enteric feeding was declined. At six months after diagnose, it was considered corticodependent, so she stopped AZA and initiated infliximab (INF) therapy. During third administration occurred an anaphylactic reaction leading to a drug switch to adalimumab (ADA), AZA and prednisolone. It was documented partial response as reactive C-protein (RCP) and faecal calprotectin continued above normal even after ten months of adalimumab therapy. It was decided to initiate Ustekinumab therapy and, after three months, RCP normalized.

None adverse events were described.

Conclusion: The limited efficacy of the current medical therapies for Crohn disease in children lead to the need of new drugs. Ustekinumab in approved for use in adult patients with Crohn disease, with proved efficacy and safety, but their use in paediatric population is still off-labelled. This case suggests that this drug appears safe and effective in young ages and can be an alternative in patients intolerant or refractory to labelled therapies.

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Inflammatory bowel disease and school absenteeism

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Objectives and Study: Inflammatory Bowel Disease (IBD) is a chronic disease with a negative impact on growth, psychosocial development, schooling of the child, and some related consequences on the quality of life. Aim: To prospectively analyze school absenteeism of children followed for IBD and to explore the causes.

Method: A prospective multicenter study of patients with IBD aged 6 to 18, from September 2016 to June 2017. The absenteeism and its causes were collected via a monthly questionnaire filled by patients, or their family, using postal mail services. The results were compared with the existing data supplied by the school authorities (comparison with 497 students divided on a class by class basis). Our study obtained the greenlight of the Ethic Committee.

Results: 140 patients presented the criteria of inclusion. 108 patients (62 boys) were included at an average age of 14.1 ± 2.6 years. There were 71 Crohn's Diseases (CD) and 37 Ulcerative Colitis (UC) or colitis unclassified with a progression pace of 2.8 ± 2.2 years. The global response rate during the school year was 83.1 %. Among the whole cohort, the patients were absent 10.8 days on average in the school year that is 4.8 ± 5.5% of the working days. The non-sick children were absent 7.2 days on average in the school year that is 3.2 ± 1.6% of the working days. The digestive disorders (diarrheas, abdominal pains, rectal bleeding) represented 34 % of the causes of school absenteeism. 27 % of the absences were following scheduled events (hospitalization, endoscopy or visit) which makes it the second cause of absence listed here, behind the digestive disorders. There was no significant difference in terms of sex or location. CD had greater absenteeism than UC (5 ± 4.8% of working days vs. 4.4 ± 6.7%, p &LT; 0.05). There was an inverse correlation between duration of illness and absenteeism (p &LT; 0.05).

Conclusion: IBD children prove to be absent more frequently than the non sick children with rates close to those reported in the literature since the introduction of biotherapies. The main cause of their school absenteeism appears to be in connection with the disease itself. The part of scheduled absenteeism (consultation and hospitalization) is quite significant. The way in which the patient's care path is organized and scheduled constitutes a priority in order to limit to the greatest extent possible the negative impact on the patient's schooling and the subsequent consequences on the quality of life.

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**Development of a systematic transition eHealth program: “Here we are - Here we come”**

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**Objectives and Study:** Transition and transfer of care are crucial periods for an adolescent with Inflammatory Bowel Disease (IBD). However, programs with specific tools to define, measure and improve patients’ transition skills are few. We have previously showed that use of eHealth among adolescents with IBD improves patient’s empowerment and thus expanding this concept would be warranted. Our aim was to develop a systematic transition program including relevant and concrete measures and tools in our established eHealth program.

**Method:** Transition and transfer needs and skills were identified reviewing the literature, as well as interviewing adult and pediatric gastroenterologists. Transition relevant validated Patient Reported Outcomes (PRO) covering the identified needs and skills were selected by a consensus group (consultants, physicians, psychologists, nurses). Selected questionnaires were translated (Cross-Cultural Adaptation) and implemented into the existing eHealth program. A transition-transfer model was agreed upon by the consensus group.

**Results:** Topics patients were expected to manage were identified: knowledge (e.g. regarding the diagnosis, medication, adherence, hospital procedures, symptoms), social life (e.g. social challenges related to the disease, whom to rely on, school/work), disease management (e.g. independently report to the doctor, recognize and react on a flare, refill of prescriptions) and taking health related well-founded decisions.

PROs selected to represent those topics included: Self-efficacy (Izaguirre 2014), Connor-Davidson Resilience Scale-10 (Campbell-Sills 2007), Response to Stress (Connor-Smith 2000) and The Self-Management and Transition to Adulthood with Treatment, STARx (Ferris 2015).

Using this information, the transition program “Here we are -Here we come” was developed. Starting at age 14, the patient has an annual one hour transition-consultation with an IBD-specialized nurse. The consultation is based on the patient’s answers to Self-efficacy, Resilience and Response to Stress, and focuses on the patient’s abilities and difficulties. The consultation consists of topic centered dialogue conversations, practical exercises related to disease, stress, fatigue, and pain management. Patients complete the questionnaire on the eHealth web-page at home before the consultation, allowing both patients and nurses to be prepared. Symptom score and medication type and dose (mg/day) is likewise filled out at the eHealth program in order to empower reporting symptoms and medication knowledge. During the routine outpatient visits, conversation is oriented towards the young 14-15 years old patient. Once the patient is 16 years old parents are left out for ½ of the consultation and at 17 years the parents are not present. At the transfer consultation (18 years old) - both the pediatric doctor and nurse and the adult gastroenterologist are present - as well as the patient and parents, to ensure a proper transfer. To evaluate the patient’s readiness to transfer the STARx is used.

**Conclusion:** The program “Here we are - Here we come” containing specific transition readiness measures and tools is implemented in an established eHealth platform. In the future, the program will be tested in the outpatient clinic.

**Disclosure of interest:** K. Carlsen: research grant MSD Denmark, research grant Tillotts Pharma M. Hald: Speaker AbbVie and Tillotts Pharma M. C. Dubinsky: Consultant Jannsen, Takeda, Abbvie, Pfizer, Celgene L. Keefer: Research grant Abbvie and Pfizer, Consultant Pfizer, Speaker Abbvie V. Wewer: research grant MSD Denmark; research grant Tillotts pharma

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Objectives and Study: To evaluate if age of onset plays a role on the long term outcome of pediatric and adult patients with inflammatory bowel disease (IBD) attending a Latin American reference center.

Method: An analytical, observational and retrospective study of a cohort of patients with IBD was carried out. Patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) between 2000-2007 at the Italian Hospital of Buenos Aires with a follow up of 10 years were included. Patients were divided according to their age at diagnosis into 3 groups Group I (GI) : < 6 years, Group II (GII): 6-17 years and Group III (GIII): 18-40 years. Exclusion criteria: monogenic/syndromic form or incomplete clinical history. The variables considered were: sex, clinical score, endoscopic score, relapses, treatment requirements, extra-intestinal manifestations, surgery and malignancy. Primary outcome was the analysis of improvement score (at the time of diagnosis and after 10 years); i.e., disease score less than or equal to that at diagnosis, for each age group.

Results: Two hundred and eighty patients were diagnosed during that time period: Pediatric 84 UC: 52 - CD: 32/young adults 196 UC: 141 - CD 55) UC 60/193: GI 8/60 / GII 31/60, CD 28/87: GI 11/28 and GII 12/28. Improved clinical score was found as follows: GI 100%, GII: 97% (31/32) and GIII 93% (40/43) (p= 0.808). Improved endoscopic score: GI 100%, GII 87.5% (28/32), GIII 90 % (39/43) (p=0.467). Perianal disease at onset: GII: 2/11 (18%), GIII 1/12 (8%) (p 0.77), 10 years: GII: 1/11 (9%). Association was found in GIII/relapse: p= 0.006 which was adjusted by type of disease (Table 1). Neither the type of IBD nor age were associated with the need of surgery. Biological Therapy: UC. GII: 2/21 (9.5%), GIII: 10/31 (32%) (P=0.073)/ CD: GII 3/11 (27%), GIII 4/12 (33%) (P=0.84). Extra-intestinal manifestations: UC: GI 37% (3/8), GII 14% (3/21), GIII 22% (7/31), CD: GI 40% (2/5), GII 9% (1/11) (p 0.037); Malignancy: UC: GI 1/8 (14%) and GII 1/21 (5%), CD.: GIII 4/12 (33%).

[Table 1: Factors associated with relapse]

Conclusion: In this cohort, children with early onset had a more benign long term outcome than those presented by young adults who showed a more relapsing course. Perhaps local characteristics and not age of onset play a role and explain these findings.
Response to combination of oral antibiotic therapy in pediatric inflammatory bowel disease. A single centre experience.

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In refractory cases of pediatric inflammatory Bowel disease, the combination of oral antibiotics therapy has been proposed as a rescue therapy. The aim of the study is to expose our experience with this medical strategy.

Methods: Retrospective analysis based on the medical reports found in a third level centre, in children diagnosed of IBD who received oral antibiotic as a rescue therapy with Doxycycline (Ciprofloxacin for < 8 years old), Metronidazole, Amoxicillin and Vancomycin. Using the variables (clinical and epidemiological) and searching the duration of the treatment and clinical response, using the Pediatric Ulcerative Colitis Activity Index, or Pediatric Crohn's Disease Activity Index, were evaluated at week 1, week 3 and week 12, and inflammatory markers (ESR, CRP) at baseline, week 1 and week 3.

Results: Six cases with moderate-severe refractory disease were included (5 Ulcerative Colitis, 1 colonic Crohn’s disease). Median age was 11.5 years (IQR 5.3-13.6), with a median disease duration of 15 months (IQR 10-39). All of them were corticosteroid-dependent (N = 4) or resistant (N = 2). 4/6 patients were refractory to anti-TNF therapy (Infliximab). Median duration of treatment was 58 days (range 3-122 days). One of the patients was discontinued after 3 days due to clinical worsening. Clinical remission (PUCAI &LT; 10 or PCDAI &LT; 12.5) was achieved in 33% (N = 2) of the cases and response in 33% (N = 2) at 3 weeks of treatment. Inflammatory markers improved in 3/6 cases at week 1, and in 4/6 cases at week 3. At 12 weeks follow-up, 83% of the patients (n=5) needed a change of therapy.

Conclusions: The combination of oral antibiotic therapy seems to be effective in the short term in some cases of refractory colonic IBD, this effect seems to be transient, requiring a different therapeutic strategy in the medium-term in most of our patients.

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Use of maintenance enteral nutrition in paediatric crohn's disease: Perspectives and practice

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Objectives and Study: Paediatric Crohn's Disease (CD) is a chronic, relapsing inflammatory condition with the potential to impact on nutritional status and growth. Maintenance enteral nutrition (MEN), in the form of oral nutritional supplements, is commonly prescribed with the presumption it will help maintain remission although there is limited evidence to confirm efficacy. The aim of this study was to investigate practice in the United Kingdom (UK) regarding the use of MEN in children and young people with CD in remission, to gain an insight into the clinical application of the existing evidence.

Method: A web-based questionnaire with both multiple choice and open text questions was distributed to all dietitians (n=23) in the British Society of Paediatric Gastroenterology, Hepatology and Nutrition Associate Members group. Responses were collated, results are reported as percentage of total responses.

Results: 19/23 (83%) dietitians responded. The majority 18/19 (95%) recommended MEN after primary induction, sixteen of whom (89%) advised MEN to be taken for as long as possible with no exit criteria. Modulen was used as first line MEN by 11/18 (61%). Energy contribution from MEN was 25-30% patient's energy requirement. The primary aim for MEN was to maintain remission 9/18 (50% dietitians) and secondary, to treat persistent faltering growth 3/18 (17% dietitians). Eight dietitians (44%) rated patients to be 60% compliant with daily MEN.

<table>
<thead>
<tr>
<th>Factors influencing compliance</th>
<th>No of responses (n=19)</th>
<th>Factors to improve compliance</th>
<th>No of responses (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste</td>
<td>13/19 (68%)</td>
<td>Different flavours</td>
<td>12/19 (63%)</td>
</tr>
<tr>
<td>Parental nagging</td>
<td>12/19 (63%)</td>
<td>Reminders from dietitian</td>
<td>5/19 (26%)</td>
</tr>
<tr>
<td>Felt bloated / nauseous</td>
<td>4/10 (21%)</td>
<td>Recipes for home made MEN</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>6/19 (32%)</td>
<td>Notify patient of long term MEN at diagnosis</td>
<td>2/19 (11%)</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>5/19 (26%)</td>
<td>Reduce taste fatigue</td>
<td>4/19 (21%)</td>
</tr>
</tbody>
</table>

[Dietetic perspectives]

Conclusions: MEN in the form of oral nutritional supplements is prescribed for as long as possible after primary induction in paediatric CD, with the goal of improving growth and maintaining remission. However, few participants identified exit criteria for MEN. Dietetic responses indicated that most perceive the major barrier to compliance with MEN was taste, with little role for food based nutrition support. Further investigation of patient and parental perspective of MEN is essential to help us deliver appropriate nutritional management with specific exit criteria for use.

Contact e-mail address: j.ashton@soton.ac.uk
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-313

Parent and patient perception of the use of maintenance enteral nutrition in Paediatric Crohn's Disease

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Objectives and Study: Nutritional management of Paediatric Crohn's disease (CD) aims to improve nutritional status, promote growth and ensure normal pubertal development. Maintenance enteral nutrition (MEN) after primary induction in the form of daily nutritional supplement drinks is commonly used. The aim of this study was to characterise child and parent perception of MEN and to consider strategies for improving compliance and acceptability.

Method: Seventy-seven children with CD and their parents who had received MEN within the last 2 years, were asked to complete a multiple choice questionnaire with additional free-text response areas. Separate questionnaires were sent to the children (aged 10 years and over) and parents to assess difference in opinion.

Results: 41/77 (53%) children and 48/77 (62%) parents responded. Daily compliance with MEN was reported by 26/41 (63%) children and 31/48 (65%) parents, influenced by medical/dietetic reinforcement (12/23 (52%) children; 8/28 (29%) parents), parental nagging (10/23 (43%) children; 9/28 (32%) parents) and bloating/nausea (7/23 (30%) children; 8/28 (29%) parents). More parents 6/28 (21%) than children 2/23 (9%) were worried that discontinuing MEN may result in relapse. Nutrient dense foods were preferable to MEN for 23/41 (56%) children and 28/48 (58%) parents.

<table>
<thead>
<tr>
<th>Suggestions to improve compliance (multiple choice)</th>
<th>Child (n=17)</th>
<th>Parent (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller volume drinks</td>
<td>11/17 (65%)</td>
<td>18/22 (82%)</td>
</tr>
<tr>
<td>Different flavours</td>
<td>8/17 (47%)</td>
<td>5/22 (23%)</td>
</tr>
<tr>
<td>Recipes for home made MEN</td>
<td>5/17 (29%)</td>
<td>8/22 (36%)</td>
</tr>
<tr>
<td>MEN that does not cause bloating/nausea</td>
<td>2/17 (12%)</td>
<td>0/22 (0%)</td>
</tr>
<tr>
<td>Frequent reminders from the dietitian</td>
<td>1/17 (6%)</td>
<td>1/22 (5%)</td>
</tr>
</tbody>
</table>

[Child/parent responses for compliance]

Conclusion: Two thirds of families reported daily compliance with MEN. Child reported compliance was primarily influenced by medical/dietetic/parental reinforcement and bloating/nausea; whereas parents reported multiple factors affected their child's compliance. Both groups reported smaller volumes and different flavours may have improved their child's compliance. There are many factors influencing compliance with MEN, however there is majority support from families for nutrient dense food based alternatives to MEN for this patient group.

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Objectives and Study: Restorative proctocolectomy (RPC) entails a number of metabolic consequences. Large intestine is the site for menaquinone production and bile acid reabsorption, therefore its total resection poses a threat of significant deficiencies in fat-soluble vitamins. None of the studies so far has described a complex report on vitamin A, E and K status in patients with ileal pouch-anal anastomosis.

Method: The study included 48 patients operated due to ulcerative colitis (UC; n=31) or familial adenomatous polyposis (FAP; n=17). Serum retinol and alpha-tocopherol levels were determined by high-performance liquid chromatography (reference values: vitamin A 300-800 ng/µL; vitamin E 5-20 µg/mL). The vitamin K status has been assessed by the concentration of uncarboxylated prothrombin (PIVKA-II) measured with the use of enzyme-linked immunosorbent assay (cut-off value 2 ng/mL). UC and FAP were diagnosed on the basis of clinical, histological and endoscopic criteria. Minimum two biopsies were taken from each subject and analyzed using Moskowitz scale in a double-blind mode; the sample with higher scaling was taken to further analysis. Pouchitis was diagnosed on the basis of pouchitis disease activity index (PDAI) ≥7 and Moskowitz scale ≥4. Chronic pouchitis was diagnosed in patients having at least three clinical episodes in the preceding 12 months of which at least one had been confirmed with endoscopy with biopsy and the next were diagnosed by endoscopy with biopsy or endoscopy without biopsy, but in the presence of characteristic signs or symptoms. None of the patients showed hemorrhagic diathesis nor bleeding from the pouch.

Results: The concentration of vitamin A below the reference range was observed in only one subject (UC; 2.1%). Values above the reference range ≥ 800 ng/µL were detected in four cases (8.2%; range 840-1082 ng/µL). None of the patients presented vitamin E concentrations below the reference range, however, 18.4% (9/49) of patients presented elevated vitamin E levels (range 20.7-27.8 µg/µL). Elevated PIVKA-II levels occurred in 57.1% (28/49) of patients studied. The PIVKA-II and vitamin A values did not differ between UC and FAP patients (respectively p=0.9394; p=0.9830). Values of vitamin E differed significantly depending on primary diagnosis p=0.0079. The inflammation of the pouch was found in 40.8% (20/49) of subjects. No statistically significant differences in vitamin E values and vitamin A levels were detected between patients with and without inflammation (respectively p=0.0540, p=0.1891). Vitamin K deficiency associated with Moskowitz scale ≥4 (OR=5.25; 95% CI 1.39 to 19.85) and PDAI ≥7 (OR=18.90; 95% CI 4.40 to 81.20). A multivariable regression model showed that none of the independent variables were useful for predicting the status of neither vitamin A, E nor K.

Conclusion: While patients after RPC have adequate vitamin A and E status, they frequently present vitamin K deficiency. The relation between vitamin K and pouchitis demands further research.
Withdrawal of thiopurines in pediatric IBD patients on combination therapy and evolution of Anti-TNF trough levels

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¹Hospital Sant Joan de Déu, Esplugues del Llobregat, Spain

Objectives and Study: Combination Therapy (CT) with monoclonal antibodies against tumor necrosis factor alpha (anti-TNFα) and thiopurines has been proved to be effective for induction and maintenance of remission in pediatric IBD (PIBD) patients. Combined immunosuppression decreases anti-TNFα immunogenicity, maintains higher serum levels and increases the durability of the clinical response. There is no consensus on the risk-benefit ratio of prolonged use of CT, and a review of current strategies is necessary. The aim of our study was to report the evolution of serum anti-TNFα trough levels after discontinuation of immunosuppressive therapy in pediatric IBD patients previously treated with CT, as well as their correlation with clinical and analytical variables.

Method: Descriptive, retrospective study based on the review of medical records. PIBD patients on CT with azathioprine (AZA) and Adalimumab (ADA) or Infliximab (IFX), in clinical and endoscopic remission, with TRA in therapeutic ranges and negative antibodies against anti-TNFα, who discontinued immunosuppressive treatment were recruited. Evolution of TRA, appearance of immunogenic reactions and loss of response, as well as their correlation with clinical evolution after change to monotherapy, were analyzed at 3, 6 and 12 months of follow-up.

Results: We included 13 patients (5 women, 10 Crohn’s disease, 3 ulcerative colitis), mean age at diagnosis 10.2 years (range: 3-15 years). After an average of 22.4 months (range: 14-50 months) of CT with AZA and anti-TNFα (6 IFX, 7 ADA), and previous confirmation of endoscopic-histological remission with therapeutic TRA (mean IFX levels 8.46 µg/ml and ADA 15.79 µg/ml), AZA was stopped. The mean follow-up of patients after changing to monotherapy was 6.5 months (range: 3-12 months). At 3 months after AZA withdrawal, 13/13 patients remained in clinical remission. At 6 and 12 months, 9/13 and 4/13 patients respectively completed follow-up, all of whom were in clinical remission. In 10/13 patients at 3 months, therapeutic TRA (mean IFX levels of 7 µg/ml and ADA 17.42 µg/ml) were observed; two patients are pending results at the time of writing the abstract and a single patient had undetectable levels and positive antibodies despite being in clinical remission. At 6 and 12 months, in 3/9 and 3/4 patients, respectively, the levels of the drug were determined, all of them being between normal range (mean IFX levels 4.25 µg/ml and ADA 11.81 µg/ml), and without detection of antibodies against them. None of the studied patients presented clinical symptoms suggestive of drugs immunogenicity.

Conclusion: The withdrawal of immunosuppressive therapy in pediatric PIBD patients on CT and clinical and endoscopic remission, and with therapeutic TRA, did not lead to clinical changes in the short term in our cohort, although drug levels monitoring could contribute to the prevention of subsequent onset of immunogenicity and secondary loss of response.
Children and young people with Inflammatory Bowel Disease in the Black British Population

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¹King’s College Hospital NHS Foundation Trust, London, United Kingdom

Objectives and Study: There are few studies on the phenotype and outcome of inflammatory bowel disease (IBD) in black British (BB) children. Studies in African-American children with IBD report that disease presents earlier. In these studies, IBD disease course was more commonly complicated with stricturing and fistulising disease in the Crohn’s disease (CD) population. The aim of this study was to characterize the clinical presentation and disease outcomes of Black-British children with IBD at a single institution in the United Kingdom.

Method: A single-centre retrospective cohort of children aged between zero and eighteen years with IBD diagnosed between January 2005 and June 2017 were identified. Data was collected using the electronic patient record system and included demographics, anthropometrics, disease classification using the PARIS criteria and outcome measures; need for biologic treatment, and time to biologic and need for surgery. Descriptive statistics are presented for comparison.

Results: A total cohort of 101 patients with IBD were included in the study (Caucasian (C) n=68, Black British (BB) n=33). The median age at diagnosis was similar (C Vs. BB)(12.7 years vs.12.92 years). In the CD population both groups had similar disease site distribution however the BB population had increased incidence of perianal disease (44.4% vs 22.2% in the Caucasian group). The PCDAI score at presentation was similar (C 23.1 vs BB 27). In ulcerative colitis the disease site and severity was also similar in both groups with pancolitis being more prevalent. 26/66 patients with IBD in the C group compared to 7/33 patients in the BB required biologic treatment but the Black British patients had a shorter time to biologic treatment of 0.56 years compared to 1.52 years in the Caucasian group. The need for surgical intervention was higher in the Black British group with 8/33 requiring surgical treatment, compared to 5 /68 in the Caucasian group.

Conclusion: The Black British population required earlier introduction to biologic treatment and had increased need for surgery compared to the Caucasian group. The 2 groups had similar ages and anthropometrics at presentation. Subanalysis of CD and ulcerative colitis patients also showed similar characterisation of disease. This study is limited by its small cohort size and currently the authors are working towards obtaining a nation-wide picture through multi-centre collaboration. The group are also working on comparing other ethnic groups. Prospective multi-centre longitudinal analysis are needed to look at the genetic, immunological, social and economic factors that could explain the subtle differences noted in this descriptive study to guide medical management.
Table of results

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>Black British</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=101</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>68 (m=31)</td>
<td>33 (m=18)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>12.67 [3.5-16.5]</td>
<td>12.962 [1.8-16.6]</td>
</tr>
<tr>
<td><strong>Anthropometrics at presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight z-score</td>
<td>-0.135 ± 1.52</td>
<td>-0.209 ± 1.69</td>
</tr>
<tr>
<td>Height z-score</td>
<td>-0.244 ± 1.12</td>
<td>-0.316 ± 1.16</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>-0.47 ± 1.49</td>
<td>-0.886 ± 1.67</td>
</tr>
<tr>
<td><strong>Disease characteristics (sub category)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>n=31 (m=11)</td>
<td>n=17 (m=9)</td>
</tr>
<tr>
<td>PCDAI at presentation</td>
<td>20 [0-55]</td>
<td>22.5 [0-65]</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>n=29 (m=20)</td>
<td>n=11 (m=7)</td>
</tr>
<tr>
<td>PUCAI at presentation</td>
<td>35.0 [0-70]</td>
<td>32.5 [15-55]</td>
</tr>
<tr>
<td><strong>Disease outcome data for the whole cohort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for biologic treatment (n)</td>
<td>26 (37% of whole group)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Time to biologic treatment (years)</td>
<td>1.52 [0.45-3.76]</td>
<td>0.558[0.18-2.57]</td>
</tr>
<tr>
<td>Need for surgery (n)</td>
<td>5 (7%)</td>
<td>8 (27%)</td>
</tr>
</tbody>
</table>

[Table of results]

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Oxidative stress in children with Inflammatory Bowel Disease and functional gastrointestinal disorders

Urszula Grzybowska-Chlebowczyk¹, Paulina Wysocka-Wojakiewicz², Martyna Jasielska², Bożena Cukrowska³, Sabina Wiecek¹, Maria Kniaźewska², Jerzy Chudek¹

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²Upper-Silesian Child Health Care Center, Katowice, Poland
³The Children's Memorial Health Institute, Warsaw, Poland

Objectives and Study: Inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease (CD), are chronic gastrointestinal diseases with unclear etiology. Recently also oxidative stress has been implicated in the disease pathogenesis and/or development. The aim of the study was to evaluate oxidative and antioxidative stress status and the risk of atherosclerotic process in children with IBD and functional gastrointestinal disorders.

Method: The prospective study included a group of 71 children diagnosed and treated for IBD in the Department of Gastroenterology, Medical University of Silesia in Katowice during a period of 2 years. There were 47 boys and 24 girls, aged from 3 to 18 years. CD occurred in 35 children (49.3%), UC in 36 children (50.7%). The control group consisted of 29 children (21 girls) diagnosed with functional gastrointestinal disorders (FGID). In all children anthropometric measurements and laboratory test were performed also intima-media complex in carotid artery was measured (IMC).

Results: The prevalence of high levels of total oxidative stress (TOS/TOC) was similar in patients with CD (77%), UC (72%) and FGID (82%). Low values of oxidative stress were more frequent in children with UC (22.2%) and CD (14.3%), than in the FGID group (6.9%) (p=0.94). Furthermore, the values of oxidative stress index (OSI) was similar in all 3 groups. Markers: TOS/TOC, TAS/TOS and OSI were not associated with the duration and activity of IBD, occurrence of ANCA, body mass index and BMI Z-score. Patients with FGID had the highest concentration of total cholesterol and LDL cholesterol. (p< 0.05). The average concentration of oxidized lipoprotein with average density (oxLDL) was lower in patients with inflammatory bowel diseases - with Crohn’s disease (213.9 ng/ml) and with ulcerative colitis (141.3 ng/ml) than among children with FGID (277.6 ng/ml) (p=0.03). Among patients with IBD, statistically significantly higher concentrations of oxLDL were recorded in patients with longer duration disease (p=0.01) and with higher concentrations of total cholesterol and HDL (p< 0.05). The highest concentration of anti-oxLDL was found in a group of children with CD (on average 8057.6 U/ml), and the lowest in children with FGID (p=0.05). In the group of children with IBD more often statistically significantly higher concentrations of anti-oxLDL were recorded among patients with longer duration disease (p=0.03). The highest average of the thickness of the carotid artery intima-media complex (IMC) was found in children with ulcerative colitis, smaller in children with Crohn’s disease and FGID (on average respectively 0.4 and 0.403 cm), but this difference was not statistically significant, and the obtained results remained within the normal range for the age of patients.

Conclusion: The obtained results did not support the hypothesis of total antioxidant capacity depletion and greater overall oxidative stress in patients with inflammatory bowel disease. Patients with IBD with a longer duration of the disease have higher concentrations of oxLDL and anti-oxLDL. However, due to the shorter duration of the disease than in adults, it is difficult to assess the impact of stress on the development of atherosclerotic processes that enhance along with age.

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Microbiota profile in newly-diagnosed paediatric Crohn’s disease: Data from a non-Western population

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2Boston University, Boston, United States
3Al Mofarreh Polyclinics, Riyadh, Saudi Arabia
4MassGeneral Hospital for Children, Boston, United States

Background and Study: The role of microbiota in Crohn’s Disease (CD) is increasingly recognized. However, most of the reports are from Western populations. Considering the possible variation from other populations, we aimed to describe the microbiota profile in children with CD in Saudi Arabia, a country “in transition” between developing and industrialized countries.

Methods: The children were Saudi nationals with a confirmed diagnosis of CD according to standard clinical-pathological criteria, and appropriate controls who have no evidence of CD or other inflammation. Tissue and stool samples were collected before any treatment from children with CD and controls. Tissue samples were taken from different parts of the colon and ileum. Stool samples were collected before bowel preparation (75%), or from the first stool passed after the start of bowel preparation (25%). All samples were frozen to -80°C till analysis. Bacterial community structure was determined using 454 pyrosequencing of bar-coded 16S rRNA genes. Statistical analysis was performed, using Python and R software and implemented to detect taxa association whose abundances were significantly different between CD and controls. Although less significantly-associated taxa may be biologically important, we reported only statistically-significant associations when the FDR-corrected p-value (q value) was < 0.05. Alpha diversity, a measure of taxa richness, was analyzed. Beta diversity, which accounts for both patterns of presence-absence of taxa and changes in their relative abundance between samples was quantified by the Bray-Curtis dissimilarity. Fisher t-test and exact permutation test to determine the p value for alpha diversity and for Non-parametric Multi-Dimensional Scaling beta diversity separation, respectively. Significance in diversity was defined by p value < 0.05.

Results: There were 78 samples (58 tissue, 20 stool) from 35 children (17 CD, 18 controls). Demographics of children with CD and the controls were similar. Significantly more abundant taxa in CD at the genus level included Fusobacterium, Peptostreptococcus, Psychrobacter, and Acinetobacter, and at the species level, Fusobacterium nucleatum, Bacteroides clarus, and Psychrobacter pulmonis. The three most significantly-depleted genera included Mitsuokella, Turicibacter, and Peptostreptococcus; whereas species included Roseburia inulinivorans, Bacteroides clarus, and Clostridium disporicum. The ratio of change in the figure indicates the mean abundance ratio between CD and control samples in mucosa and stool at family and genera levels.
However, as stressed in the literature, it is still not clear whether this association is the cause or the result of inflammation. Alpha diversity was significantly reduced in stool (p=0.03) but not in mucosa samples (p=0.31). Beta diversity showed difference in community composition between control and CD samples.

**Conclusion:** We found a microbiota profile similar to Western literature, suggesting a minimal role in ethnicity and a more important role of recent socioeconomic and dietary changes in this population.

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-319

Change of treatment modalities over the last 10 years in paediatric patients with inflammatory bowel disease in Switzerland

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²University Children’s Hospital of Bern, Bern, Switzerland
³Children’s Hospital of Lucerne, Luzern, Switzerland
⁴University Children’s Hospital of Zurich, Zürich, Switzerland

Introduction and aims: During the last decade several new drugs were approved for treatment of paediatric inflammatory bowel disease [IBD]. We aimed to evaluate if and how pharmacologic treatment options for paediatric IBD in Switzerland have changed over time.

Methods: Data from the paediatric Swiss IBD Cohort Study [SIBDCS] were analysed. The paediatric SIBDCS is a national prospective cohort study that was initiated in 2006. Patients were divided into two groups: patients with IBD diagnosis until 2009 (168 patients), and patients with IBD diagnosis in 2010 and after (210 patients). Both groups were analysed regarding past and current therapies as well as need for any surgery.

Results: A total of 378 paediatric IBD patients was analysed of which 51.9% had Crohn’s disease [CD], and 48.1% had ulcerative colitis / indeterminate colitis [UC / IC]. Mean age at diagnosis was 12 years. The majority (65.4%) of UC patients suffered from pancolitis at diagnosis while 45.4% of CD patients presented with ileocolonic disease at diagnosis. All patients needed corticoid treatment during their disease course. Immunomodulators were used more frequently and earlier in CD patients compared to UC patients. Prescription of 5-aminosalicylic acid for CD patients was dramatically reduced by half after the year 2010 (33.5% vs. 67.7%). A significant shift towards earlier use of biologicals could be shown in the time period of 2010 and later compared to the interval before 2010 (p< 0.001). However there was no significant decrease of surgery rate after 5 years of disease in paediatric CD patients when comparing both time groups (19.1% before 2009 versus 16.2% after 2010, pvalue 0.819). The surgery rate after 5 years of disease of all IBD patients together did not differ in both time periods with about 11%.

Conclusion: In the last decade, a trend towards an earlier use of anti-tumor necrosis factor alpha agents in paediatric IBD patients has been observed. Despite this change, no steroid sparing effect or reduction of surgery rate has occurred in Swiss paediatric IBD patients.
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-321

Impact of fecal calprotectin measurement for the diagnosis of inflammatory bowel disease in children with alarm symptoms

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1Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey

Objectives and Study: Fecal calprotectin (FC) is a neutrophil-derived protein released in stool in response to mucosal inflammation. It is simple, cheap and non-invasive test that correlates with bowel inflammation. The aim of this study was to establish whether FC measurement may be useful in children with alarm symptoms (AS) to differentiate inflammatory bowel disease (IBD) from other gastrointestinal disorders.

Method: The study included 88 consecutive patients (10.2 ± 6.1 years old, 51.1% F) who underwent colonoscopic examination for gastrointestinal symptoms. Demographic features, as well as symptoms and abnormal laboratory findings (ALF) including anemia, hypoalbuminemia (< 3.5 g/dL), high C-reactive protein (>1 mg/dL) and erythrocyte sedimentation rate (>20 mm/h) and positive FC (>70 mg/kg) was recorded. 40 patients have AS (such as; rectal blood loss, family history of IBD, weight loss, extraintestinal symptoms and perianal lesions) suggesting IBD.

Results: IBD was confirmed in 20 patients, and 16 patients had lymphonodular hyperplasia, 14 had non-specific colitis, 10 had allergic colitis. Colonoscopy was normal in 20 patients. The sensitivity, specificity, positive and negative predictive value (PPV, NPV), area under receiver operation curve (AUROC) of AS, ALF and FC is shown in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS (n=40)</td>
<td>65</td>
<td>60.29</td>
<td>32.5</td>
<td>85.4</td>
<td>0.626</td>
</tr>
<tr>
<td>AS with normal LF (n=23)</td>
<td>35</td>
<td>76.47</td>
<td>30.43</td>
<td>80</td>
<td>0.557</td>
</tr>
<tr>
<td>AS + ≤ 2 ALF (n=37)</td>
<td>55</td>
<td>61.76</td>
<td>29.73</td>
<td>82.35</td>
<td>0.584</td>
</tr>
<tr>
<td>AS + &gt; 2 ALF (n=3)</td>
<td>10</td>
<td>98.53</td>
<td>66.67</td>
<td>78.82</td>
<td>0.543</td>
</tr>
<tr>
<td>AS + FC &gt; 70 mg/kg (n=16)</td>
<td>50</td>
<td>91.18</td>
<td>62.5</td>
<td>86.11</td>
<td>0.706</td>
</tr>
<tr>
<td>AS + FC &gt; 150 mg/kg (n=12)</td>
<td>40</td>
<td>94.12</td>
<td>66.67</td>
<td>84.21</td>
<td>0.671</td>
</tr>
</tbody>
</table>

[Impact of FC on the diagnosis of IBD (n=88)]

Specificity, PPV, NPV and AUROC are higher in FC measurements compared to other laboratory parameters.

Conclusion: Adding FC measurement in patients with symptoms suggesting IBD is useful and reliable. Higher levels are associated with higher probability of IBD.

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Vol. 66, Supplement 2, April 2018
Inflammatory Bowel Disease incidence in South Moravian Region (Czech Republic), 2002-2016

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Objectives and Study: Inflammatory bowel disease is considered a global disease in the 21st century. Studies worldwide have shown an increase in incidence in paediatric population. The aim of the study was to detect the rising incidence of IBD in paediatric population (approximately 240 000) over a 15-year period in the South Moravian Region of the Czech Republic. Another objective was to characterize differences by sex, age and to determine the future projection of incidence of IBD in the region and, by extension, the whole Czech Republic.

Methods: In the Czech Republic, the treatment of paediatric IBD is centralized into hospitals that provide tertiary care. University Hospital of Brno is one of the gastroenterology centres that provides a complex treatment of IBD patients. We evaluated 321 consecutive paediatric IBD patients < 19 years of age in the South Moravian region (one of the 14 regional units in the Czech Republic). They all had been diagnosed according to the relevant guidelines.

Results: We evaluated 321 patients with IBD: 167 of them had Crohn's disease (52.0%), 114 had ulcerative colitis (35.5%) and 40 were IBD-unclassified (12.5%). Among all the cases of IBD, 53.8% were males. The average age of a diagnosed person was 13.37 years (95%CI: 12.97-13.76) and the patients went an average of 7.59 months (95%CI: 6.15-9.03) between the first symptoms and the diagnosis. The overall incidence of IBD significantly increased from 2.84 per 100 000 person-years in 2002 to 12.54 per 100 000 person-years in 2016 (P = 0.012).

Conclusions: Our results show that the overall incidence of paediatric IBD is increasing. These data highlight the need for a further research to identify the possible risk factors of IBD development.

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Objectives and Study: The aim of this study was to investigate the clinical features and the frequencies of extraintestinal manifestations (EIMs) in paediatric inflammatory bowel disease (IBD) and to see the related factors with the development of EIMs.

Method: The medical data of the IBD patients were reviewed retrospectively from June 2010 to July 2017. Baseline demographic findings, Paris classifications, Paediatric Crohn's Disease Activity Index (PCDAI) and Paediatric Ulcerative Colitis Activity Index (PUCAI) scores, CRP, ESR, faecal calprotectin, BMI and the specific diagnosis of EIMs were investigated. The secondary extraintestinal complications and the complications of medication were excluded.

Results: Total of 172 patients were enrolled, of whom 137 (79.7%) were Crohn's disease (CD), 35 (20.3%) were Ulcerative colitis (UC). The mean age at the diagnosis was 13.65 ± 3.03 years for CD, 12.71 ± 3.11 years for UC, and the mean follow-up duration was 4.05 ± 2.88 years for CD, 3.27 ± 2.28 years for UC. The EIMs occurred in 40 patients (23.3%), which were consisted of 34 (85%) in CD and 6 (15.0%) in UC, respectively. EIMs were arthritis or arthralgia (n=15, 37.5%), Stomatitis and/or oral ulcer (n=10, 25%), hepatitis (n=5, 12.5%), pancreatitis (n=2, 5%), nephritis (n=4, 10%), erythema nodosum (n=2, 5%), ankylosing spondylitis (n=1, 2.5%), and pyoderma gangrenosum (n=1, 2.5%). The Paris classification for CD did not show any significant difference between EIM and non-EIM group, but those for UC showed a significant difference in severity (p=0.032). The PCDAI and PUCAI scores were not significantly different between the EIM and non-EIM groups, in CD and UC, respectively.

Conclusion: The EIMs were not significantly related with the diagnosis age, gender, diagnosis, disease location, behavior or extent in the paediatric IBD patients. The disease severity of UC was significantly related with the occurrence of EIMs.

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Faecal calprotectin is capable of predicting mucosal healing in paediatric-onset Crohn’s disease patients under sustained clinical remission with biologics

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Objectives and Study: Despite the emergence of mucosal healing (MH) as a major therapeutic goal in Crohn’s disease (CD), its feasibility into real-life practice is limited, especially in the paediatric population. We aimed to investigate whether faecal calprotectin (FC) may serve as a surrogate marker of predicting MH in paediatric-onset CD patients under sustained clinical remission with biologics.

Method: This study was a cross-sectional study conducted at the Department of Pediatrics of two tertiary hospitals in Korea from July, 2015 to June, 2017. Patients included in the study were (1) paediatric-onset CD patients diagnosed before the age of 19, (2) were under sustained clinical remission for at least 6 months with biologics, and (3) had simultaneously performed ileocolonoscopies and FC as well as other laboratory tests. The correlation between Simple endoscopic score for Crohn’s disease (SES-CD) and FC levels, as well as the association between MH and FC were investigated. Furthermore, the cut-off level of FC in predicting MH was derived. Complete MH was defined as SES = 0, and partial MH was defined as SES-CD < 3.

Results: A total 99 patients (65 males, and 34 females) were included in this study. FC levels were significantly higher in patients who had achieved complete MH (median 34.1 vs. 514.3 µg/g, \( P < 0.001 \)), and also who had achieved partial MH (median 38.5 vs. 710.5 µg/g, \( P < 0.001 \)), respectively. SES-CD scores and FC levels showed a significant correlation (\( \rho = 0.71, \ P < 0.001 \)). According to logistic regression analysis, \( FC^{*10^{-2}} \) was the only factor associated with both complete MH (OR = 0.47, 95% CI = 0.31-0.63, \( P < 0.001 \)), and partial MH (OR = 0.62, 95% CI = 0.5-0.73, \( P < 0.001 \)), respectively. According to receiver operating curve analysis, cut-off levels of FC in predicting complete MH and partial MH were 97.9 (AUC = 0.907, 95% CI 0.844-0.969, sensitivity 88.2%, specificity 87.5%, PPV 87.5%, NPV 88.2%, \( P < 0.001 \)) and 122.4 (AUC = 0.904, 95% CI = 0.842-0.967, sensitivity 79.7%, specificity 94.3%, PPV 71.7%, NPV 96.2%, \( P < 0.001 \)), respectively.
Conclusion: FC is capable of predicting mucosal healing in paediatric-onset CD patients under sustained clinical remission with biologics. The role of FC may increase in the treat-to-target era, especially in children with CD.

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Factors associated with the development of immunogenicity to anti-tumour necrosis factor agents in paediatric inflammatory bowel disease patients

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Objectives and Study: It is well known that the development of anti-drug antibodies (ADAs) to anti-tumour necrosis factor (TNF) agents may cause a decrease in serum anti-TNF agent levels and consequently loss of response. However, relevant data is limited in the paediatric population of inflammatory bowel disease (IBD). We aimed to investigate factors associated with the development of immunogenicity to anti-TNF agents in paediatric patients with inflammatory bowel disease receiving biologics.

Method: This study was a cross-sectional study conducted at the Department of Pediatrics of Kyungpook National University Children's Hospital from March, 2017 to July, 2017. We obtained sera from 59 patients who were under maintenance treatment with infliximab (IFX) or adalimumab (ADL), and ADA levels as well as trough levels were checked by commercial enzyme-linked immunosorbent assay kits. ADA >10 AU/mL was defined as ADA positive, and sub-therapeutic trough levels (TLs) for IFX and ADL were defined as < 3 and < 5 µg/mL, respectively. Factors associated with ADA positivity were investigated by analyzing clinicodemographic, laboratory, and treatment related factors.

Results: Among the 59 patients [49 with Crohn's disease (CD), and 10 with ulcerative colitis (UC)], 48 and 11 patients were under treatment with IFX and ADL, respectively. ADAs were positive in 6 patients (10.2%). Comparison between ADA positive and negative patients revealed statistically significant differences in white blood cell (WBC) counts (median 8300 vs. 6210 /µL, \( P = 0.001 \)), and the proportion of patients with sub-therapeutic TLs (17% vs. 83.3%, \( P = 0.001 \)). According to multivariable logistic regression analysis, diagnosis with UC and WBC counts were independently associated with the development of ADAs (OR = 10.48, 95% CI = 1.14-132.07, \( P = 0.042 \) and OR = 2.58, 95% CI = 1.42-5.89, \( P = 0.006 \), respectively). According to receiver operating curve analysis, the optimal cut-off level of predicting ADA positivity were 6930 /µL for WBC count (AUC = 0.897, 95% CI = 0.796-0.997, sensitivity 100%, specificity 73.8%, \( P < 0.001 \)), and 3.48 µg/mL for IFX TLs (AUC = 0.917, 95% CI = 0.815-1.000, sensitivity 100%, specificity 76.2%, \( P < 0.001 \), respectively.)
Conclusion: WBC counts and IFX TLs may predict the development of ADAs during treatment with anti-TNF agents. Further large-scale studies are required in order to clarify whether immunogenicity to anti-TNF agents are more likely to occur in children with UC compared to those with CD.

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Psychosocial aspects of inflammatory bowel disease in children

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Objectives and study: The aim of the study was to compare the quality of life, the presence of depression and anxiety disorders in children with inflammatory bowel disease IBD and healthy controls. The second aim of the study was to compare anxiety and depression of patient’s parents and parents of healthy children.

Design of the study was reviewed and approved by the institutional Ethics Committee.

Methods: Twenty-seven pediatric patients with IBD (17 children with Crohn’s diseases - CD and 10 with ulcerative colitis - UC) were enrolled to this comparative cross-sectional study. 23 patients were in disease remission and 4 showed mild disease activity. They were compared with the control group of 39 healthy children of the same age (13-16 years-old).

We analyzed parameters of quality of life (questionnaire KidScreen-10), a presence of depression (questionnaire CDI - Children’s Depression Inventory) and anxiety disorders (questionnaire SAD - The Scale of Anxiety in Children). The parents completed questionnaires BAI (Beck Anxiety Inventory), BDI-II (Beck Depression Inventory, second version) and PedsQL (Pediatrics Quality of Life) Family Impact Module.

Results: There were no statistically significant differences between QoL assessed using KidScreen-10 in IBD children and controls (38.82±8.58 vs. 38.24±4.76, n.s.). However, the QoL of parents of children with IBD was significantly lower than QoL of parents of healthy controls (PedsQL total scores in mothers 66.84±14.78 vs 76.17±14.65, p<0.05 and in fathers 68.86±16.35 vs 81.74±12.89, p<0.01).

The mothers of the IBD patients were significantly more anxious (BAI scores 9.50±10.39 vs 5.26±4.75, p<0.05) and the fathers more depressed (BDI scores 7.23±6.50 vs 3.64±3.51 p<0.05) than the parents of the controls, but there was no difference in the levels of anxiety (SAD scores 29.25±6.28 vs 29.59±4.31, n.s.) or in depression (CDI scores 45.86±35.54 vs 38.76±28.53, n.s.) between IBD adolescents and the controls.

Conclusion: No difference in the QoL, incidence of depression or anxiety in children with IBD compared to healthy controls was found. The fathers of the IBD patients were more depressed, and the mothers were more anxious, than parents of healthy children. There were significantly lower scores of the QoL in the parents of the adolescents with IBD, than in the parents of the healthy controls. It seems, that the parents of IBD patients restricted their live needs, because of their chronically ill children.

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G-P-327

Multi-centre experience of vedolizumab use in paediatric patients with Inflammatory Bowel Disease

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Objectives and Study: Efficacy and safety of vedolizumab, has been demonstrated in trials involving adults diagnosed with Inflammatory Bowel Disease (IBD). In children, it is being used in some selected cases in whom conventional therapy failed, as off-label use. The aim of this study is to investigate the efficacy and safety profile of vedolizumab treatment in paediatric patients with IBD.

Method: Spanish multicenter observational trial, involving paediatric patients with IBD that have received treatment with vedolizumab. The percentage of remission, clinical activity and analytical parameters were analysed at week 6, 14, 30 and 52. Every adverse effect during treatment was recorded.

Results: 14 patients were included (9 male, 7 CD). In CD patients, 57% showed growth delay and 14% had penetrating phenotype. In UC patients, 100% had pancolitis, and 87.5% showed severe activity. Considering analytical parameters, CRP values decreased from 4.3 (± 1.2) at the beginning to 2.2 (± 0.8) at week 14 and 0.13 at week 30. ESR, albumin, haemoglobin, iron and calprotectin also improved. There was initial response at week 6 in 71.4% of UC, whereas in CD this was 28.6%. At week 14, in CD patients this increased to 57%, and in UC it remained in 71.4%. At week 30, 6 patients were still on treatment (3 CD), maintaining response 2 of the CD patients (1 remission), and 3 of the patients with UC. 50% of patients experienced side effects, being more serious in CD.

Conclusion: Vedolizumab was effective in a high percentage of patients refractory to anti-TNF, and it seems to be more effective as induction therapy in UC than in CD patients. Some adverse reactions were observed in CD patients. More prospective trials are needed to determine efficacy and security of this drug in paediatric population.
Risk factors associated with complicated behavior occurrence in pediatric Crohn’s disease

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Objectives and Study: The disease behavior is most important predictor of having surgery in pediatric Crohn's Disease (CD). Progression towards a stricturing or a penetrating behavior will be happen to the majority of pediatric CD with non-stricturing, non-penetrating behavior at diagnosis. This study is aimed to classify risk factors of disease behavior changes in pediatric CD.

Method: We retrospectively analyzed 592 patients who were younger than 18 years of age at CD diagnosis between 1987 and 2013. They were classified according to the Paris classification and followed-up for 20 years after diagnosis. The cumulative probabilities of developing complicated behavior and associations between risk factors and behavior changes were evaluated.

Results: At the time of diagnosis, 88.8% had non-stricturing, non-penetrating disease, and 9.4% had stricture disease and 1.8% had penetrating disease. Male gender, younger age (0-< 10 years of age at diagnosis), perianal fistula were significantly higher in non-complicated behavior. Among 509 patients with non-complicated behavior at diagnosis, 159 (31.2%) changed their behavior. In multivariate analysis, non-colonic location and younger age (0-< 5 years of age at diagnosis) were associated with an increased risk of behavior changes. The cumulative probabilities of developing complicated disease behavior at 1, 5, and 10 years after diagnosis were 13.5%, 56.0%, and 85.0%, respectively.

Conclusion: Almost one-third changed their behavior. Non-colonic location and younger age were associated with increased risk of behavior changes. Different to other studies, perianal fistula and sex had no association with behavior changes.
Value of magnetic resonance enterography in diagnosis and treatment follow up in Crohn's disease in children

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Background: Crohn's disease is an unspecific inflammatory disease which can affect all parts of the gastrointestinal tract. Magnetic resonance enterography (EMR) enables detection of pathologic changes in the small intestine, which is not accessible to endoscopic study.

Objectives and Study: The objective of the work was an analysis of the changes in the small intestine Crohn's disease in children - their activity, clinical manifestation and treatment effects.

Method: EMR was performed in 108 children aged 5.5 to 18 years (x=13.7 years), 40 girls and 68 boys with Crohn's disease, diagnosed according to the Porto criteria. Location and clinical manifestation was classified according to the Paris classification. EMR was done according to the Giles protocol. In all the children gastroscopy and colonoscopy were carried out. Clinical activity of disease was assessed using PCDAI and endoscopic activity using SES-CD. Additionally, serum C-reactive protein, fecal calprotectin and body mass index (BMI) were measured. In 36 children (33.3%) control EMR was done, after 21 months on average.

Results: The most frequent location of disease was the colon (41.7%), terminal ileum and colon (24.1%) and ileoacetacal region (13.9%). Inflammatory manifestation of the disease was dominant - 81.5%; structuring -12.9% and structuring and/or penetrating 5.6%. In EMR in 40.8% of the children inflammatory changes were diagnosed and in 11.1% stricturing changes in the small intestine. Control EMR, performed in 36 children, after treatment with immunomodulating drugs and/or biological therapy (anti TNF alfa), demonstrated improvement in 55.5% of the children and remission in 16.7%. In these children clinical improvement was observed in 66.7% (assessed by PCDAI, serum CRP and fecal calprotectin).

Conclusion: EMR allows for demonstration of changes in the small intestine and for assessment of treatment results in children with Crohn's disease. EMR was safe and well tolerated by the children.

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A case of de novo Inflammatory Bowel Disease (IBD) post thymic transplant in a patient with Di George syndrome

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Objectives and Study: Children who develop de novo Inflammatory Bowel Disease (IBD) have been described following organ transplantation involving the liver, kidney and haematopoietic stem cells. This occurs despite the concomitant use of immunosuppressive agents. To the best of our knowledge this has not been described following thymic transplantation. Clinical outcome of children undergoing thymic transplantation have generally been good with exception of autoimmune complications such as Transient Nephritis, Thyroiditis, Chronic Autoimmune Haemolytic Anaemia (CAHA) and Idiopathic Thrombocytopenia Purpura (ITP).

Method: We present for the first time a case of de novo Crohn's disease 6 months post thymic transplantation in a 17-month old male with a complete Di George syndrome.

Results: A 17 month old Maltese boy with genetically confirmed Di George syndrome with phenotypic features of Tetralogy of Fallot, dysmorphic features, hypoparathyroidism and feeding difficulties underwent a thymic transplant at the age of 6 months. He received immunosuppression with Cyclosporin pre- and post-transplantation, along with antithymocyte globulin and Methylprednisolone. 6 months after thymic transplantation he developed perianal rash, bloody diarrhoea, vomiting and weight loss, with a raised calprotectin > 1000 mg/kg. Endoscopic examination revealed oedematous fragile mucosa with contact bleeding and patchy erythema with a histological evidence of granulomatous chronic active colitis with focal apoptosis in keeping with Crohn's-like changes. In order to avoid systemic steroid use and loss of engrafted thymic Treg cells initial therapy with metronidazole and budesonide was chosen with good clinical response and rapid return of bloody diarrhoea on cessation of budesonide therapy. A decision was made to use an exclusive enteral feed with an amino acid formula (Neocate junior®) for duration of 8 weeks with clinical remission. Food reintroduction has commenced and repeat endoscopy is planned in the coming months. Other causes of the granulomatous colitis were excluded including infectious diarrhoea and graft versus host disease.

Conclusion: This is to the best of our knowledge the first case of de novo IBD reported in a child undergoing thymic transplantation. De novo IBD may represent a new autoimmune phenomenon and will need to be further explored.
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-332

Severe colitis as initial symptom of granulomatosis with polyangiitis (GPA)

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Objectives: Granulomatosis with polyangiitis (GPA) is a small to medium vessel vasculitis mostly affecting the upper respiratory tract, lungs, and kidneys. Most patients are positive for anti-neutrophil cytoplasmic antibodies (ANCA) with proteinase 3 (PR3) specificity. Gastrointestinal involvement and colitis are rare in GPA. Here, we report two GPA patients with inflammatory bowel disease (IBD).

Results: A 15-year-old boy presented with weight loss, bloody diarrhea, arthritis, skin vasculitis, fever, fatigue, and elevated inflammation markers (ESR, CrP). Colonoscopy and esophagogastroduodenoscopy revealed severe pancolitis and esophagitis with multiple circular ulcerative lesions. The patient was positive for xANCA and anti-PR3 antibodies. Additional investigations uncovered renal and pulmonary involvement (ground glass infiltrates). The diagnosis GPA was made and therapy with corticosteroids and cyclophosphamide, followed by methotrexate and cotrimoxazole was started. Remission was reached within three months and sustained to date (12 months).

Another 17-year-old boy, was referred to our hospital with watery and bloody diarrhea, and significant weight loss (25% of his body weight). Colonoscopy showed severe pancolitis with extensive involvement of the terminal ileum. Prior to referral, the patient had been treated for Crohn's disease in a community hospital. However, colitis was refractory to treatment with oral prednisolone, methylprednisolone pulse therapy, azathioprine, and infliximab. Patient's history included additional symptoms of nasal septum defect and epistaxis. Further investigation unveiled nasal granulomatous inflammation, pulmonary (ground glass infiltrates), renal involvement (immune-complex nephritis), and positivity for anti-PR3 antibodies. Induction therapy with cyclophosphamide and high-dose corticosteroids was initiated, followed by methotrexate and cotrimoxazole treatment. Symptoms improved continuously, but complete remission was not reached (mild diarrhea remained) within six months, and the family withdrew from treatment.

Conclusion: GPA is a rare cause of IBD. Severe IBD can distract from additional symptoms that need to be considered and weighted in an interdisciplinary approach with pediatric gastroenterologists, radiologists, and rheumatologists. Mucosal vasculitis is present in a subset of IBD patients, but biopsies often fail to contain submucosal tissue, and vasculitis may therefore be missed. Recently, we reported a significant proportion of “classical” pediatric IBD patients to be positive for anti-PR3 antibodies. Based on these observations, we propose that a PR3-positive vasculitis may be a common feature in a spectrum of disorders presenting with IBD. Future research is needed to investigate the pathogenic relationship of IBD and vasculitis. Since most therapeutic agents used in IBD can also be effective in vasculitis, GPA may, at least initially be missed. Unfortunately, delayed diagnoses and insufficient treatment of GPA may result in more severe clinical courses and failure to reach full and stable remission. Thus, detailed patient history (including ENT symptoms, rashes, etc.) is essential, and GPA should be considered as a potential cause for colitis, especially in unusual or treatment refractory cases.

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Introduction: Treatment with thiopurines is frequently used to maintain remission in Pediatric Inflammatory Bowel Disease (PIBD). Under immunosuppression, primary Epstein-Barr virus (EBV) infection has been associated with severe hematological complications.

Methods: Retrospective study of hematological complications occurring in our PIBD patients treated with AZA secondary to primary infection by EBV. Clinical and analytical parameters at onset of infection, treatment strategy and outcomes were collected.

Results: 6 patients (4 Ulcerative Colitis (CU), 2 Crohn's Disease (CD)). Mean age at primary EBV infection 15.5 years (Range 13-18). Symptoms at presentation: fever (100%), adenopathies (100%) and sore throat (66%). Mean duration of fever before being investigated 8.16 days (Range 3-10 days). Mean baseline PCR EBV load was 7.628 copies/ml (Range 265-16.954 copies/ml). Leukopenia was present in all the patients (Range 1300-2600/mm³); mean absolute neutrophils count 134 (Range: 500-1700). In all patients ferritin levels were evaluated, being high (>150 ng/ml) in 83.3% patients. Lactate dehydrogenase (LDH) was assessed in 4/6, showing high values (>70 UI/L) in 100%. 5/6 patients required hospital admission. 1/6 was performed a bone marrow biopsy to exclude hemophagocytic syndrome, with normal results. Intravenous Ganciclovir was initiated in all patients (mean duration: 17 days; Range 7-21 days). None of the patients developed hemophagocytic syndrome or lymphoma. AZA was discontinued in 5/6. In one patient intravenous gammaglobulins were added and was maintained with 5-ASA (rejection to start anti-TNF). Other CD patient started anti-TNF on monotherapy with good response. AZA was re-started in the other 3 patients after EBV viral load negativization, without complications. In one patient AZA dose was decreased.

Conclusions: Pediatric patients on thiopurine treatment and primary infection by EBV are at risk for develop myelotoxicity that can be severe. In our patients, antiviral treatment and suppression or decrease of AZA doses seems to be an strategy to avoid major complications.

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Switching from originator (Remicade) to biosimilar (Remsima) infliximab for maintenance of remission in paediatric inflammatory bowel disease is effective

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Objectives and Study: Following its UK launch for all indications in 2015, the safety, efficacy and cost-effectiveness of biosimilar infliximab in adult inflammatory bowel disease (IBD) has now been extensively shown from real-world experiences and meta-analysis. Limited paediatric IBD-specific data has shown similar safety and efficacy in the induction setting, with only preliminary results available for patients switching from originator to biosimilar. We now report prospective clinical safety and efficacy data for patients from across two PIBD networks switching from originator to biosimilar infliximab.

Method: Prospective clinical data was collected for 18 paediatric IBD patients from the South East and West Scotland regional services, switched from originator to biosimilar infliximab for disease maintenance. Electronic patient records, case notes and laboratory reports were used to analyse disease activity scores, blood and faecal biomarkers, adverse events and disease flares over a minimum post switch period of 6 months. Patients were routinely given hydrocortisone prior to each infusion, as before switching.

Results: There were 18 patients with IBD, including 13 Crohn's disease (CD), 3 ulcerative colitis (UC) and 2 IBD unclassified (IBDU). 10 were on co-immunosuppression with azathioprine and 2 with methotrexate. At the time of switch, the median ages were CD 16.6 years (14.5 - 17.3), UC 11.7 years and IBDU 16.4 years. The median time on infliximab prior to switching was 2.1 years (1.6 - 4.6). 2 patients were classified as having mild disease and 16 as being in remission using disease scores at baseline.

By 6 months, 1 patient's disease had changed to mild, 1 had improved to remission and 1 patient in remission had a mild flare but was returned to remission by 6 months without need for rescue treatment. There were also no clinically significant changes in biochemical markers (p>0.05), with median serum albumin changing from 39.5 g/L (37 - 41) at baseline to 38 g/L (37.5 - 39.5) only. No infusion reactions were recorded from a total of 91 infusions. The median infliximab trough level at baseline was 3.9 (Range 1.3 - 6.2); at 6 months, this was 3.8 (2.1 - 6.8), dose escalation was however performed for 8 patients during the initial follow-up period. In the 14 patients who had antibodies collected pre and post switch, 0/14 had a significant change in their antibody status.

By 12 months, 13 patients remained on Remsima, 3 were electively stopped due to disease remission, 1 was switched to adalimumab and 1 was lost to follow-up. Of the 13 patients continuing treatment, 1 patient had mild disease activity and the rest were in remission. Again, no clinically significant changes in biochemical markers were found either (p>0.05), with a recorded median serum albumin of 38 g/L (35.5 - 39).

Conclusion: Switching from originator infliximab to the biosimilar appears not to be associated with any increase in infusion reactions or significant loss of efficacy in the short term. Studies looking at longer term loss of efficacy and immunogenicity are now needed.

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Evaluation and management of adrenal suppression in paediatric inflammatory bowel disease (IBD) patients on long term corticosteroids

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Objectives and Study: Corticosteroid therapy is often used to induce remission or control flares in children with inflammatory bowel disease (IBD). However, prolonged courses of steroids predispose patients to adrenal suppression. Patients with adrenal suppression may have nonspecific symptoms including fatigue, headache, loss of appetite, weight loss and nausea which may be missed or mistakenly attributed to inflammatory bowel disease. There remains a lack of data in the evaluation and management of adrenal suppression in paediatric IBD patients on long term corticosteroids. The aim of the study is to review our single centre’s experience in the evaluation and management of adrenal suppression in paediatric IBD patients on long term corticosteroids.

Method: Data of all paediatric IBD patients who had cortisol levels and subsequently synacthen tests from February 2008 to October 2017 in a tertiary paediatric gastroenterology unit were extrapolated from Infoflex database, Cerner Millennium, endocrine database and biochemistry log. Patient demographics, diagnosis, duration of corticosteroid treatment, early morning cortisol levels, synacthen test results and management were analysed.

Results: Data expressed as median (range)

Over an 8.5-year period, there were only 5 children annually who had morning cortisol levels but in total only 11 children required a synacthen test.

3/11 cortisol < 20 nmol/l
8/11 cortisol 73.5 nmol/l (29 to 190 nmol/l)

Disease distribution: Ulcerative colitis n=6 (5 pancolitis, 1 distal colitis)
Crohn’s disease n=5 (4 ileocolonic, 1 left-sided colitis)

M to F ratio 7:4.
Age at diagnosis: 10.5 years (2.5 - 15.8 years)
Age of first synacthen test: 16 years (7 - 19 years)
Duration of steroid: 13 months (3 - 38.5 months)

The standard in-house protocol following prolonged steroids and low morning cortisol level was to switch oral prednisolone to oral hydrocortisone and then undergo a synacthen test after 2-3 months (n=9).

7/11 children had normal synacthen test and their oral hydrocortisone dose or oral prednisolone dose were easily weaned.
4 children with abnormal results did not wean with repeat synacthen tests at median of 7.5 months (range 6 - 9 months). The repeat synacthen tests were normal with ultimate successful weaning of oral hydrocortisone.

One exception was a child with a history of prolonged steroid use who had an ileal resection for stricturing disease. She had been steroid free for 5 months. She developed an Addisonian crisis with cortisol level 29 nmol/l postoperatively responding to intravenous hydrocortisone and required maintenance oral hydrocortisone 5mg TDS for 3 months before a synacthen test.

Conclusion: We recommend that all children with prolonged steroid course should have a morning cortisol level measured when the dose of oral prednisolone is tapered down to 5mg daily. If cortisol level is low we recommend conversion to oral hydrocortisone followed by formal synacthen test at 2-3 months.

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**Analysis of family history of autoimmune conditions in paediatric Inflammatory Bowel Disease**

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\(^3\)University of Southampton, Southampton, United Kingdom

**Objectives and Study:** Paediatric inflammatory bowel disease (PIBD) is immune-mediated, occurring in genetically susceptible individuals, with environmental factors contributing to the development of disease. Studies have identified a genetic overlap between PIBD and other autoimmune diseases. This study aimed to observe the family history (FH) of autoimmune diseases, including IBD, in family members of children diagnosed with PIBD.

**Methods:** FH of IBD and other autoimmune disease was prospectively collected in patients recruited to the genetics of PIBD study at Southampton Children's Hospital over a three year period from January-2014 to December-2016. Data included two or more generations per family. Specific diseases asked about were Crohn's disease (CD), ulcerative colitis (UC), asthma, autoimmune thyroid disease, coeliac disease and psoriasis. Data are presented as percentages of individuals with a FH (of disease). Statistical analysis was with the Chi-squared test.

**Results:** 130 children were recruited; 57 female, 73 male. Median age at diagnosis; 13.27 years. 76 (58%) had CD, 38 (29%) had UC and 16 (12%) were diagnosed with IBD Unclassified. There was a higher incidence of Crohn's disease in male versus female patients (70% vs 40% respectively, \(p=0.004\)).

FH of autoimmune disease is shown in table 1 († significant difference between Crohn’s disease and ulcerative colitis (p=< 0.05). Considering all children with IBD there was a positive family history for asthma in 39.2%, autoimmune thyroid disease in 16.2%, psoriasis in 13.1% and coeliac disease in 9.2%.

Of those patients with a FH of IBD, patients with CD had double the frequency of a FH of CD compared to a FH of UC (31.6% vs 17.1%, \(p=0.006\)). Patients with UC were three times more likely to have a FH of UC compared to CD (29.0% vs 10.5%, \(p=0.006\)). In patients with IBDU there was no difference between a positive FH of CD or UC (both 18.8%). There was no difference between children with CD, UC or IBDU in the overall probability of having a positive FH of (any type of) IBD. Of the patients with a positive FH of IBD (n=47), 19.1% (n=9) had a FH of both CD and UC.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Total cases of illness</th>
<th>Number of families affected</th>
<th>Mean number of cases per family affected</th>
<th>Percentage of all patients with a family history of disease (n=130)</th>
<th>Percentage of males with a family history of disease (n=73)</th>
<th>Percentage of females with a family history of disease (n=57)</th>
<th>Percentage of probands with Crohn's disease with a family history of disease (n=76)</th>
<th>Percentage of probands with ulcerative colitis with a family history of disease (n=38)</th>
<th>Percentage of probands with IBDU with a family history of disease (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All IBD</td>
<td>73</td>
<td>46</td>
<td>1.65</td>
<td>36.2%</td>
<td>37.0%</td>
<td>33.3%</td>
<td>40.8%</td>
<td>29.0%</td>
<td>31.3%</td>
</tr>
<tr>
<td>CD</td>
<td>37</td>
<td>31</td>
<td>1.19</td>
<td>23.8%</td>
<td>23.3%</td>
<td>24.6%</td>
<td>31.6%†</td>
<td>10.5%†</td>
<td>18.8%</td>
</tr>
<tr>
<td>UC</td>
<td>36</td>
<td>27</td>
<td>1.33</td>
<td>20.8%</td>
<td>20.6%</td>
<td>21.1%</td>
<td>17.1%†</td>
<td>29.0%†</td>
<td>18.8%</td>
</tr>
<tr>
<td>Asthma</td>
<td>126</td>
<td>51</td>
<td>2.47</td>
<td>39.2%</td>
<td>37.0%</td>
<td>42.1%</td>
<td>40.8%</td>
<td>36.8%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>37</td>
<td>21</td>
<td>1.76</td>
<td>16.2%</td>
<td>17.8%</td>
<td>14.0%</td>
<td>15.8%</td>
<td>15.7%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>24</td>
<td>17</td>
<td>1.41</td>
<td>13.1%</td>
<td>13.7%</td>
<td>12.3%</td>
<td>14.5%</td>
<td>10.5%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Coeliac</td>
<td>13</td>
<td>12</td>
<td>1.08</td>
<td>9.2%</td>
<td>8.2%</td>
<td>10.5%</td>
<td>10.5%</td>
<td>5.3%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
Conclusions: Patients with a diagnosis of CD or UC are more likely to have a family history of that type of IBD. FH of autoimmune disease is common in children diagnosed with IBD with over 1/3 of patients having a positive family history for IBD or asthma. This study highlights the genetic burden of autoimmune diseases within the families of children diagnosed with IBD. Further work is needed to look for joint susceptibility genes/variants contributing to development of both autoimmune conditions and IBD.

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**Objectives and Study:** One-fifth of patients with Crohn disease (CD) have no response at all to all kinds of anti-TNF and an additional one-third eventually fail to therapy. Despite increasing use of anti-TNF in children with CD, long-term durability and safety of the drug beyond 1 year is limited. We evaluated the long-term durability of anti-TNF maintenance therapy in pediatric CD followed over 1 year at a single tertiary hospital in Korea.

**Method:** A single-center retrospective study of 75 pediatric CD patients who had been treated with anti-TNF more than one year between 2005 and 2016 was done. Anti-TNF outcomes were defined as sustained remission in the absence of dose modification (sustained durable remission), recaptured response, and treatment failure. Sustained durable remission was defined as remission with standard maintenance infliximab dosing of 5 mg/kg administered at a frequency of every 8 weeks.

**Results:** The male/female ratio of patient was 41:34. The median age of the patients was 13.95 years. Six patients (8.0%) had a family history of IBD among first-degree relatives. The disease location of CD was L1 in 4 (5.3%) of the patients, L2 in 11 (14.7%), and L3 in 60 (80.0%). L4A and L4B were diagnosed in 30.0% and 54.8% of patient, respectively. The clinical behavior was B1 in 57 (77.0%) of the patients, B2 in 15 (20.3%), B3 in 0 (0.0%), B23 in 2 (2.7%), and P in 34 (46%). The mean duration of anti-TNF treatment was 1,218.43±753.04 days. Sixty five (86.7%) patients were treated with anti-TNF and immunomodulator. The response to anti-TNF treatment was as follows: sustained durable response 50 (66.7%), no durable response 25 (33.3%), recaptured response 11 (14.7%), and treatment failure 14 (18.7%). Pediatric Crohn disease patients receiving anti-TNF had a higher rate of L3 (P=0.004), B2 (P=0.004) and luminal surgical treatment (P=0.000) compared with anti-TNF naïve patients. Long-term anti-TNF responders had a higher rate of L4B (P=0.036), a lower rate of diarrhea (P=0.014) and younger age at diagnosis (P=0.024). Female gender was a risk factor of treatment failure to anti-TNF (P=0.002). Serious infectious complications (multi-drug resistant pulmonary tuberculosis, acute pyelonephritis and herpes zoster) occurred in 7 (9.3%) of patients during anti-TNF treatment.

**Conclusion:** The majority of pediatric CD patients treated with anti-TNF (66.7%) in this study showed sustained clinical benefit during a median follow-up of 38 months. The patients with no durable response to anti-TNF treatment, optimization with potential immunosuppressive co-treatment and dose or administration interval adjustment of the anti-TNF was needed.
**Objectives and Study:** Defects in the interleukin (IL)-10 pathway underlie the pathology of an important subgroup of very early-onset Crohn's disease (CD). As a cytokine, IL10 plays an important anti-inflammatory role in mucosal homeostasis and the defect of its receptor (IL10R) A and B also develop CD. We report five cases of early-onset CD in a single center.

**Method:** The clinical characteristics of the five children with severe early-onset CD were reviewed retrospectively. Whole exome sequencing (WES) were conducted for the five children with refractory inflammatory bowel disease (IBD). For a functional validation of deleterious variants in IL10RA, singal transducer and activator of transcription 3 (STAT3) phosphorylation was measured in IL-10 stimulated peripheral blood mononuclear cells by western blot analysis.

**Results:** The mean age of CD onset of the five children with IL10RA deficiency was 1.5 year and four were girls. All the children showed severe activities in Paediatric Crohn’s Disease Activity Index. On the WES, compound heterozygotes of R101W, T179T, and Y91C IL10RA variants were identified. All the patients showed the defect in STAT3 phosphorylation by IL-10 stimulation. During the follow-up, three had colectomy and ileostomy and two died of recurrent colitis and sepsis. One patient with T179T homozygote had hematopoietic stem cell transplantation and showed the clinical remission during 1 year post transplantation.

**Conclusion:** We report a single-center experience of IL10RA deficiency in early-onset CD. Due to lacks of functional validation of some listed IL10RA variants in database, functional study is still important in the diagnosis of IL10RA deficiency.
Predictive value of ASCA and pANCA for surgical risk in Korean paediatric patients with Crohn’s disease and ulcerative colitis: a single center experience

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Objectives and Study: The aim of this study is to evaluate the effect of anti-Saccharomyces cerevisiae antibodies (ASCA) and neutrophil specific nuclear autoantibodies (pANCA) as a predictive value for surgical risk in Korean paediatric patients with Crohn’s disease (CD) and Ulcerative Colitis (UC).

Method: Medical record of 594 children with CD and 211 with UC who had been diagnosed before the age of 18 from January 2000 to December 2013 in a single center were retrospectively reviewed. Among them, serologic tests for ASCA IgA and IgG, and pANCA were implemented, and the primary outcome was surgery according to disease course.

Results: Among children with CD, 29.7% (N=117) of the patients underwent surgical therapy such as ileostomy and bowel resection. In multivariate analysis, surgery was associated with ASCA IgA (OR = 12.11; p = 0.001) and both positivity of ASCA IgG and IgA (OR = 12.142; p = 0.002); while a single positivity of either ASCA IgG or pANCA was not associated with surgery in the patients with CD. Among children with UC, 9% (N=19) of the patients had gone surgical operation such as total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) with ileostomy and total colectomy. However, neither ASCA IgG/IgA nor ANCA was associated with surgery in the patients with UC.

Conclusion: ASCA IgA and IgG were associated with surgery during the disease course in Korean paediatric patients with CD, but not with UC. Therefore, ASCA may be an important factor in predicting surgical outcome in Korean paediatric patients with CD. Further studies to determine the cut off level of ASCA antibodies in predicting clinical outcomes are warranted.
Objectives and Study: The incidence of paediatric inflammatory bowel disease (IBD) is rising, but IBD appears to have certain particularities in Romania in comparison to western countries. We aimed to characterize the phenotype and early disease course in paediatric patients younger than 6 years, in comparison to older children.

Method: We conducted a retrospective study from 2004 to 2015 which included children diagnosed with IBD in the Paediatric Gastroenterology Department of "Grigore Alexandrescu" Emergency Children's Hospital in Bucharest, Romania. We reviewed medical records of all the patients and we analyzed the clinical features and diagnostic tests at the moment of diagnosis and 2 years after (the third year of evolution).

Results: We identified a number of 57 patients with IBD, out of which 5 were excluded (incomplete data). Fifty two patients were included in the study. The mean age of the study group at diagnosis was 9 years 6 months. Thirty-nine patients had ulcerative colitis (UC), while 13 had Crohn's Disease (CD). Patients were divided in two groups - very early onset paediatric IBD (VEO-PIBD) and late onset paediatric IBD (LO-PIBD). Thirty-three percent were diagnosed before 6 years of age and were included in the VEO-PIBD group - most of them with UC (82.3%), fewer with CD (17.7%). Sixty seven percent were diagnosed after 6 years of age and were included in the LO-PIBD group - 28.6% with CD and 71.4% with UC. Out of the patients diagnosed with UC, the ones in the VEO-PIBD group had pancolitis more frequently than the ones in the LO-PIBD group (50% vs. 36%). We report more severe forms of disease at diagnosis in the VEO-PIBD group - 2 patients with CD and 2 with UC, out of which one died. After 2 years the majority of the patients with VEO-PIBD (70%) were in remission or had mild forms of the disease. In the LO-IBD group, 64% of the patients with UC had moderate-severe forms at diagnosis, and 32% were still having moderate-severe flares in the third year of evolution. In the same group 80% of the patients with CD had moderate-severe disease at diagnosis - after 2 years for only half of them remission was obtained, the other half (4 patients) still had moderate-severe flares.

Conclusion: UC was more frequent than CD in both groups, especially in VEO-PIBD. In the VEO-PIBD group we report very severe cases, even though most of the forms are mild, in comparison to the LO-PIBD group.
Study on the infection of toxigenic clostridium difficile in pediatric inflammatory bowel disease patients

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Objectives and Study: Inflammatory bowel disease is a group of diseases, which affect children's nutrition, growth and even threaten the lives. Some adults' studies found that patients with IBD are at increased risk of developing C. Difficile infection, have worse outcomes, including higher rates of colectomy and death, and higher rates of recurrence. C. Difficile infection may be involved in the pathogenesis and activity of IBD. But there were few reports about the children with IBD. This study choose the children with IBD as the research object. We intend to learn the clonization of the toxigenic C. Difficile in the region s of children by detecting the C. Difficile toxin genes of feces from children with IBD.

Method: Collecting 30 cases of the hospitalized patients diagnosed with IBD(15 with UC, 15 with CD) and 30 cases of the healthy children of the department of health care in July 2015 to October 2016. We gather their feces and clinical data. Extracted DNA with fecal genomic DNA extraction kit, and then detected C. Difficile toxin genes including the genes for pathogenicity locus (tcdA, tcdB, tcdC, tcdD, tcdE) and the genes for binary toxin CDT (cdtA and cdtB) using PCR method.

Results:
1. 7(11.7%) specimens were tested positive for Clostridium difficile in the 60 stool specimens. 6 cases(20.0%) with IBD, 3 cases(20.0%) with UC and 3 cases(20.0%) with CD. In healthy controls, 1 case(3.3%) of C. Difficile toxin-positive(P&LT; 0.05).
2. Of the 7 positive specimens, 6(85.7%) were A+B-, 1(14.3%) were A+B+. TcdC, tcdD, tcdE positive specimens were 1(14.3%), 2(28.6%), 3(42.9%), gene mutation was not found by sequencing.
3. 3 (20%) specimens were tested positive in UC with 1 cases of early onset and 2 cases of relapsing. 3 specimens were all in disease activity with 1 case of mild activity and 2 cases of moderate activity(P&LT; 0.05). There were not detected positive C. Difficile toxin in E1, 1 case in E2, and 2 cases in E3.
4. 3 (20%) specimens were tested positive in CD. 3 specimens were all of relapsing and in disease activity with 1 case of mild activity and 2 cases of moderate-severe activity. There were not detected positive C. Difficile toxin in L1, 1 case in L2, and 2 cases in L3(1 case also had upper gastrointestinal lesion). There were 2 cases detected positive C. Difficile toxin in B1(1 case also had perianal lesion), 1 case in B2, and not detected in B3.
5. To analysis the clinical data of the cases with the C. Difficile toxin-positive in IBD group, aged 1 year and 2 month to 15 years and 3 month. The shortest course of disease was 15 days with abdominal discomfort and hematochezia and others characterized by recurrent abdominal pain and hematochezia sharply. The treatment of IBD differ, 3 cases of hormone, 1 case of Mesalazine, 1 case of Sulfasalazine, 1 case of Infliximab. The child of C. Difficile toxin-positive feces samples of healthy control didn't have gastrointestinal symptoms.

Conclusion:
1. Patients of IBD of C. Difficile infection rate is higher than healthy children.
2. C. Difficile infection in patients of UC may coincide with disease activity.
3. For patients of IBD with sudden onset or exacerbation of the disease, without common bacterial infections and irregular use of drugs, should also pay attention to the presence of C. Difficile infection and give targeted treatment timely.

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Chronic granulomatous disease mimicking Crohn’s disease

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Objectives and Study: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease caused by mutation in any of the genes encoding subunits in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex present in many cells including phagocytes. The hallmark of CGD is recurrent bacterial and fungal infections and granuloma formation. CGD tends to present before the age of five and is more common in boys as two third of cases are inherited in a X- linked recessive mode. The gastrointestinal manifestations are relatively common in patients with CGD. However, gastrointestinal manifestation as initial presentation of CGD is very rare and has been reported in only 5% of cases. The gastrointestinal symptoms seen are weight loss, failure to thrive, loose stools, bowel obstruction, perianal ulcerations, fistula, rectal bleeding, anaemia, hypoalbuminaemia and colitis. These can mimic Crohn’s disease. We present siblings who were initially diagnosed and treated with Crohn’s disease and a few years later were diagnosed with CGD. The diagnosis of CGD was particularly challenging, as the presentation was atypical.

Method: Retrospective notes reviews of two patients using the Infoflex database and Cerner Millennium.

Results: Both female patients presented age five and half and there was no history of recurrent infections. Both siblings had minimal macroscopic findings on upper and lower endoscopy but extensive microscopic finding of granulomatous inflammation. The younger sibling subsequently developed hepatosplenomegaly and had a complete work up including a normal nitroblue tetrazolium test. Her liver biopsy revealed granulomatous inflammation. As part of the COLORS study an abnormality was detected and further genetic analysis confirmed the diagnosis of CGD. The two siblings with CGD had a mild phenotype mimicking Crohn’s disease initially. The gene abnormality identified in both cases was p22phox mutation that is inherited in autosomal recessive mode. Of interest parents are consanguineous.

Conclusion: The mild phenotypic disease with profuse granulomatous inflammation should raise the suspicion of alternative diagnosis including CGD even in the absence of recurrent infections or in cases where the disease presents unusually and is refractive to mainstay treatment. We suggest early genetic testing for CGD.

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Lactase deficiency in children with Inflammatory Bowel Disease (IBD)

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¹Federal State Autonomous Institution 'National Medical Research Center of Children's Health' of the Ministry of Health of the Russian Federation, Moscow, Russian Federation

Objectives and Study: Lactase deficiency (LD) can occur in case of the damage of the small intestine mucosa or genetic predisposition. The aim of the study is to determine the rate of LD in children with inflammatory bowel diseases (IBD) with the purpose of correcting diet therapy.

Method: The study involved 146 children aged 1-17 years; with Crohn’s disease (group 1, n=72) and ulcerative colitis (group 2, n =74). All children had no obvious clinical signs of LD. Lactase activity was determined by semiquantitative «Lactose Intolerance quick test» in biopsies of jejunum mucosa obtained during gastroscopy. The test is based on the ability of the bioptate to break down lactose to glucose and galactose; glucose content is estimated using the chromogen. Assessment of the condition (severe, moderate hypolactasia, or normal lactase activity) was made by means of a 20-minute color reaction data compared with those given in the attached (encased) chromatic plate.

Results: The most pronounced disorders were observed in patients with Crohn’s disease, with predominant involvement of the small intestine.
In group 1, normolactasia was observed in 20 children (28%), moderate hypolactasia in 24 (33%) and severe hypolactasia in 28 (39%) of cases.
In group 2, normolactasia was observed in 27 children (36%), moderate hypolactasia in 22 (30%), and severe hypolactasia in 25 (34%) of cases.
Based on the test results, lactose-free or low lactose diet was recommended to the patients with moderate to severe lactose intolerance.

Conclusion: The preliminary results on the frequency of LD in children with IBD showed that there is an urgent need to study the lactase activity in order to optimize diet therapy in this group of patients. Further studies are also needed to clarify the clinical significance of the Lactose Intolerance quick test results and their correlation with the clinical manifestations of lactase deficiency.

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Clinical patterns and outcomes of Very-Early-Onset Inflammatory Bowel Disease (VEOIBD) - A single centre experience

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¹Hospital Sant Joan de Déu, Esplugues del Llobregat, Spain

Objectives and Study: The term Very Early Onset IBD (VEOIBD), describes intestinal inflammation presenting in children younger than 6 years. It usually presents with extensive disease, greater colonic involvement, and aggressive clinical course. Our objective is to describe our experience with VEOIBD patients.

Method: We included all VEOIBD patients diagnosed in our centre (2002-2016). Baseline characteristics, clinical patterns, treatment and long-term evolution were collected.

Results: 24 patients (15 boys) were included. Mean age at diagnosis, 33 months (range: 8-64m). The most frequent symptoms at presentation were diarrhoea (100%), rectal bleeding (95%), abdominal pain (54%) and weight loss (54%). Mean time of diagnostic delay 5.5 months (1-18m). Anaemia was present in 58%, increased ESR and/or CRP in 41% and hypoalbuminemia in 12.5%. Pancolonic involvement was the most frequent finding. Eighteen patients (75%) showed a pattern suggestive of UC, 3 of CD and 3 were classified as IBDU. Severity at onset was moderate-severe in 75%. Four patients had concomitant liver disease, one arthritis and one vasculitis. Induction treatment included salicylates (18), steroids (11) and anti-TNF (4). Exclusive enteral nutrition was used in 2 with CD-like pattern, being effective in one. Immunomodulators were initiated at diagnosis in 13 patients. During the evolution, 4 patients needed escalation to anti-TNF. Vedolizumab was used in 2 after anti-TNF primary failure. Colectomy was performed in 5 (20%), in one case more than ten years after diagnosis. Only one of our patients was diagnosed with a specific non-classical-IBD disease (X-linked immunodeficiency), although we have recently included all the other patients in a wide-genetic study to rule out other forms of monogenic diseases, results pending.

Conclusion: VEOIBD present with extensive colonic involvement, moderate to severe activity, and aggressive behavior. Immunological and genetic studies are recommended to exclude specific immunological diseases of similar presentation that can benefit from a different therapeutic approach.
Continued statural growth in older adolescents and young adults with Crohn’s disease and ulcerative colitis beyond the time of expected growth plate closure

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Background: Statural growth, a dynamic marker of disease activity, is commonly impaired in pediatric Crohn’s disease (CD), but not ulcerative colitis (UC). Delayed bone age (BA) is common in CD; its frequency in UC is unknown. Bone age measurements facilitate clinically meaningful interpretation of statural growth. Growth plates close at bone age (BA) 15 years in females (F) and 17 in males (M). Delayed skeletal maturation results in delayed closure of growth plates and continued growth potential. The aim of this study was to determine [1] the frequency of continued growth beyond the time of expected growth plate closure in a large cohort of patients with pediatric CD and UC and [2] the total height gain and years of additional growth after baseline to achieve final adult height in the patients exhibiting continued growth.

Methods: We identified all F ≥ chronological age (CA) 15 years and M ≥ CA 17 years with CD and UC in the ImproveCareNow registry who had height documented at ≥ 3 visits at least 6 months apart. We defined continued growth as height gain ≥1.0 cm after CA 15 years in F’s and 17 in M’s (baseline). Fisher’s exact test, Kaplan-Meier estimates, and log-rank tests were utilized.

Results: 3011 patients (48% F; 76% CD; 24% UC) met study criteria. See Table for detailed results. 2143 (71%) patients manifested continued growth, which was more common in CD than UC and in CD F’s than CD M’s. In patients who continued to grow, median CA at which final adult height was achieved was 18.8-19.0 years in M’s and 16.9-17.1 years in F’s; median final adult height was 178.6-182.5 cm in M’s and 165.0-166.2 cm in F’s. Median final adult height was greater in UC M’s than CD M’s. Median height gain was 2.1-2.5 cm in M’s and 2.1-2.8 cm in F’s. CD F’s achieved greater height gain from baseline than UC F’s.
**Conclusions:** In the largest cohort of older adolescents and young adults with IBD reported to date, our results support that patients with IBD may continue to grow beyond the expected time of growth plate closure. Continued growth is more common in CD than in UC and more common in CD F’s than CD M’s. A novel finding is that a high proportion of patients with UC exhibit continued growth, suggesting delayed BA is common in UC. These data highlight the need for prospective longitudinal studies to examine BA progression and statural growth in patients with CD and UC.

**Disclosure of interest:** Gupta, N. Financial support for research: Celgene contributed funding to support this study Sylvester, F. Consultancy: LANDOS Inc Colletti, R. Consultancy: Abbvie, Janssen Biotech, Accordant Health Services

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**Table**

<table>
<thead>
<tr>
<th>Patients with Continued Growth [Percent (N)]</th>
<th>( \text{CD} ) (N=2282)</th>
<th>( \text{UC} ) (N=729)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males vs Females</td>
<td>73% (1662) vs 71% (879) M</td>
<td>66% (481) vs 65% (209) M</td>
<td>.0004</td>
</tr>
<tr>
<td>Males vs Females</td>
<td>75% (783) F</td>
<td>65% (272) F</td>
<td>.753</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final Adult Height (cm) [Median (95% CI)]</th>
<th>( \text{CD} )</th>
<th>( \text{UC} )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>178.6 (177.8, 179.3)</td>
<td>182.5 (180.5, 184.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Females</td>
<td>165.0 (164.4, 165.6)</td>
<td>166.2 (165.4, 167.4)</td>
<td>.152</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronological Age at Which Final Adult Height Was Achieved (Years) [Median (95% CI)]</th>
<th>( \text{CD} )</th>
<th>( \text{UC} )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>18.8 (18.7, 19.0)</td>
<td>19.0 (18.7, 19.1)</td>
<td>.636</td>
</tr>
<tr>
<td>Females</td>
<td>17.1 (17.0, 17.3)</td>
<td>16.9 (15.7, 17.2)</td>
<td>.111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years of Additional Growth Beyond Baseline to Achieve Final Adult Height [Median (95% CI)]</th>
<th>( \text{CD} )</th>
<th>( \text{UC} )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1.8 (1.7, 2.0)</td>
<td>2.0 (1.7, 2.1)</td>
<td>.636</td>
</tr>
<tr>
<td>Females</td>
<td>2.1 (2.0, 2.3)</td>
<td>1.9 (1.7, 2.2)</td>
<td>.111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height Gain from Baseline (cm) [Median (95% CI)]</th>
<th>( \text{CD} )</th>
<th>( \text{UC} )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2.5 (2.3, 2.7)</td>
<td>2.1 (1.9, 2.6)</td>
<td>.113</td>
</tr>
<tr>
<td>Females</td>
<td>2.8 (2.5, 3.0)</td>
<td>2.1 (1.8, 2.4)</td>
<td>.0002</td>
</tr>
</tbody>
</table>
Bone mineral density and nutritional status at diagnosis of inflammatory bowel disease in paediatric patients

Etna Masip¹, Ester Donat¹, Begoña Polo¹, Mercedes San Felix², Carmen Ribes-Koninckx¹

¹Pediatric Gastroenterology and Hepatology Unit, Valencia, Spain
²Nurse from Pediatric Gastroenterology and Hepatology Unit, Valencia, Spain

Objectives and Study: Inflammatory bowel disease (IBD) is known to be a risk factor for osteopenia and osteoporosis. It has a multifactorial pathogenesis and it is supposed to be present at very early stages of the disease although data in paediatric series at diagnosis are scarce. The aim of the study is to evaluate the status of bone mineral density (BMD) and the nutritional status at diagnosis of IBD in our paediatric population.

Method: Retrospective review of all pediatric patients referred to our unit for diagnosis of IBD in the last 5 years. The BMD is performed at the time of diagnosis with dual x-ray absorptiometry (DXA) on lumbar spine in all patients and is expressed by z-score. Additional demographic data were collected: weight, height, score index at diagnosis and fecal calprotectin.

Results: 33 patients were included. 63% Ulcerative Colitis (UC), 37% Crohn's Disease (CD). Mean (±SD) age at diagnosis of IBD was 11.24 (±2.17) years. The median BMD z-score was -0.1 (interquartile range: -1.1 to +0.25), which is the normal rate in general population. Osteopenia defined as z-score ≤ -1SD was found in 33% of the patients (n=11), and osteoporosis defined as z-score ≤ -2.5SD was found only in 1 patient (3%) with a severe CD (PCDAI 38) at diagnosis. No fractures were observed at diagnosis of IBD.

There were no significant differences between UC and CD patients regarding: age at diagnosis (p=0.98), weight and height at diagnosis (p=0.1608, p=0.57), fecal calprotectin (p=0.42), and BMD (p=0.12). Based on activity scores at diagnosis UC patients have more severe illness (PUCAI 35-60 in 75%) than CD ones (PCDAI 10-27 in 50%).

The characteristics baseline of patients with osteopenia at diagnosis of IBD showed no statistically difference in: gender, UC or CD, fecal calprotectin and height. Only the weight and body mass index were significant (p=0.03) (Table 1). Median weight z-score at diagnosis was -0.6 (interquartile range -1.7 to +0.2) for patients with osteopenia, versus a median of 0 (interquartile range -1 to +1) in patients with normal bone status. Using multivariable logistic regression analyses, a slightly positive correlation (r= 0.09) was found between the weight z-score and the DXA z-score at diagnosis of IBD: lower z-score for weight correlated with more osteopenia based on DXA z-score.

<table>
<thead>
<tr>
<th></th>
<th>OSTEOOPENIA</th>
<th>NORMAL BMD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>10.64±2.9</td>
<td>11.55±1.68</td>
<td>0.26</td>
</tr>
<tr>
<td>Male Gender (n, %)</td>
<td>6 (54.5%)</td>
<td>15 (68.2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td>3035.6±2720.8</td>
<td>2105.5±1571.9</td>
<td>0.22</td>
</tr>
<tr>
<td>Ulcerative Colitis (n, %)</td>
<td>5 (45.5%)</td>
<td>15 (68.2%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Crohn's Disease (n, %)</td>
<td>6 (54.5%)</td>
<td>7 (31.8%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Weight at diagnosis</td>
<td>32.37±9.3</td>
<td>41.2±11.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Height at diagnosis</td>
<td>141.54±18.4</td>
<td>148.6±12.5</td>
<td>0.20</td>
</tr>
</tbody>
</table>

[Characteristics of patients with osteopenia and no]

Conclusion:
- Osteopenia but not osteoporosis is present at diagnosis in pediatric IBD patients. These being naïf patients, no treatment related side effects can be accounted for our findings.
- There is no difference in BMD between CD and UC patients at diagnosis.
- The median z-score BMD approximates to normal population rates at diagnosis.
- Low weight at diagnosis correlating, in our patients, with low BMD, it can thus be considered as a risk factor for osteopenia.

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Can we predict mucosal inflammation in children with inflammatory bowel disease without colonoscopy?

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**Objectives and Study:** Faecal calprotectin (FC) is a good marker in monitoring mucosal healing in adults with inflammatory bowel disease (IBD). Its concentrations in faeces is related to state of mucosa observed in endoscopy. Only few studies in paediatric IBD patients concern the role of FC in mucosa status assessment. The aim of the study was to determine the of cut-off points for FC levels in children with IBD corresponding to the severity of inflammation lesions observed in colonoscopy.

**Method:** 167 patients with IBD (F 73, M 94), of which 97 had ulcerative colitis (UC) and 70 had Crohn’s disease (CD) were involved to the study. All had colonoscopy performed and FC level within a week before endoscopy measured. Mucosa status was assessed with Mayo score for UC and Simple Endoscopic Score for CD (SES-CD). We have identified three subgroups: those with mucosal healing and Mayo score 0 or SES-CD 0-2, patients with mild inflammation in gut mucosa defined as Mayo score 1 or SES-CD 3-6, those with moderate inflammation described as Mayo score 2 or SES-CD 7-15 and finally those with sever disease with Mayo score 3 or SES-CD >15. The ROC was used as a statistical method to establish cut-off points. The AUC assesses the differentiation quality of the study group. We also analysed other laboratory, clinical or demographic data to established their impact on state of mucosa.

**Results:** Strong significant positive correlation between Mayo score or SES-CD and FC was found with r=0.66. We also found low positive significant correlation between endoscopy findings and C-reactive protein (r=0.38), platelets (r=0.38) and erythrocyte sedimentation rate (r=0.27) and low negative significant correlation with inflammation degree and haematocrit (r=0.36) and body mass index (r=0.22). AUC for FC in differentiation between mucosal healing and mild disease was 0.73, between mild and moderate inflammation was 0.75, whereas between moderate and sever endoscopy findings was 0.67. The optimal cut-off levels of FC of discrimination between subgroup with mucosal healing and low disease activity, low and moderate inflammation, finally moderate and sever disease was: 77 µg/g with sensitivity 0.56 and specificity 0.81, 367 µg/g with sensitivity 0.67 and specificity 0.81 and 1214 µg/g with sensitivity 0.58 and specificity 0.80 respectively.

**Conclusion:** FC is a good marker of mucosal healing in children with IBD and it is closely related to endoscopy findings. Using FC we can predict degree of inflammation in paediatric patients, however discrimination between patients with moderate and sever lesions is not satisfactory. Further efforts are need to find more effectiveness model or marker, that determine degree of endoscopic activity in children with IBD.

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The interrelationship between hepcidin, vitamin D and anemia in children with inflammatory bowel disease- A preliminary study

Hadar Lev¹, Tut Galai¹, Ronit Lubetzky¹, Anat Yerushalmy Feler¹, Shlomi Cohen¹

¹Dana Dwek Children’s Hospital, Tel Aviv Medical Centerewk Children Hospital, Tel Aviv, Israel

Objectives and Study: Hepcidin is master regulator of iron metabolism. It has been shown that vitamin D suppresses hepcidin expression. Our aim was to examine the association between hepcidin, vitamin D and anemia in children with IBD.

Method: A prospective study was performed on naïve, newly diagnosed IBD patients. Control group consist of healthy children. Mild IBD patients were treated with 4000 unit of vitamin D, daily, for 2 weeks. Between- and within-group differences in iron biomarkers, 25-hydroxyvitamin D (25(OH)D), inflammatory markers (CRP, IL-6, Hepcidin) and hemoglobin concentrations at baseline and 2 weeks were determined.

Results: Forty- four children (25 IBD patients and 19 controls, 59% female /41% male, mean age 12.9±3.7 years) were recruited. Table 1 depicts the baseline laboratory data of the IBD patients and controls. At baseline, serum concentrations of hepcidin were significantly higher and 25-OHD, iron and hemoglobin were significantly lower in IBD patients compared to controls (34.2 ng/ml, 25 ng/ml, 25.5mcg/dl, 11.6 g/dl compare to 11.1 ng/ml,30 ng/ml, 73.5 mcg/dl, 13 g/dl, respectively p< 0.05). Eleven children were treated with 4000 unit of vitamin D. After 2 weeks plasma hepcidin concentration decreased by 70.7%, CRP decreased by 83% and vitamin D increased by 17% (p< 0.05)

Conclusion: Hepcidin is involved in the pathogenesis of iron restrictive anemia in children with IBD. High dose vitamin D treatment decreased CRP, IL-6, Hepcidin levels and showed a trend to increase iron levels within 2 weeks. We suggest that vitamin D may have a role in regulating iron recycling by change in pro-inflammatory markers.

Laboratory data

<table>
<thead>
<tr>
<th></th>
<th>IBD Patients n=25</th>
<th>Control n=19</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (g/dl)</td>
<td>11.6 (10.9-12.9)</td>
<td>13 (12.6-13.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>36 (35-39.5)</td>
<td>39 (36-41)</td>
<td>0.04</td>
</tr>
<tr>
<td>Iron (mcg/dl)</td>
<td>25.5 (16.7-49.7)</td>
<td>73.5 (43.2-109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>266 (239-291.5)</td>
<td>271 (244.5-343)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hepcidin (ng/ml)</td>
<td>34.2 (21.3-44.7)</td>
<td>11.1 (3.02-18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>6.2 (1.8-12.4)</td>
<td>2.5 (0.8-7)</td>
<td>0.04</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>25 (20.5-31)</td>
<td>30 (25-40)</td>
<td>0.02</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>16 (5-38.5)</td>
<td>0 (0-5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT (10e3/µL)</td>
<td>339 (265.5-379.5)</td>
<td>291 (243-332)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

[Laboratory data of IBD patients and controls]

Contact e-mail address: hadarlev6@gmail.com
Inflammatory bowel disease teams working in partnership with out of hospital healthcare providers improve patient experience

Annette Mulcahy¹, Dawn Genders², Lee Demuth², Rafeeq Muhammed¹

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²Healthcare at Home Ltd, Burton-on-Trent, United Kingdom

Objectives and Study: Many patients with chronic conditions like inflammatory Bowel Disease (IBD) prefer to receive high quality healthcare close to where they live. However many specialist services including paediatric IBD care are provided only in very few centres in the UK. Healthcare at Home Ltd, a provider of healthcare out of hospital settings, has started enhanced nursing care services in April 2017 for patients with Crohn’s disease (CD) managed in our hospital receiving treatment with Humira (Adalimumab). This service is funded by Abbvie, manufacturer of Humira. Patients who opt-in to receive this service receive nurse visits at home 2-3 weeks prior to their hospital appointments. During these visits, nurse will review Humira administration, collect blood and stool samples as requested by the hospital team, measure height and weight and complete history aspect of disease activity scores. Blood and stool sample are transported to the hospital within few hours and the clinical information is passed on to the hospital team securely within one day. The aim of this project is to assess the patient and parent satisfaction of enhanced nursing care service offered to patients with Crohn's disease on treatment with Humira.

Method: We sent patient/parent satisfaction survey questionnaires via post in August 2017 to the 29 patients registered for enhanced nursing care service. The completed questionnaires were returned to Healthcare at Home team. Parents and patients were asked to complete the survey questions independently.

Results: 16/29 (55%) families returned the completed survey questionnaires. Majority of patients and parents reported the enhanced nursing care service very helpful. Nurse review of Humira administration, the options to have bloods taken at home and the results available prior to the clinic visit have been rated highly by both patients and parents. They have found it easier to make decisions about treatment changes because of the timely availability of results prior to clinic visit. Details in Table1.

<table>
<thead>
<tr>
<th></th>
<th>Parents in agreement n (%)</th>
<th>Patients in agreement n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction with the enhanced nursing care service</td>
<td>16/16 (100%)</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Nurse visit and Humira administration review added value to my care</td>
<td>13/16 (87%)</td>
<td>10/14 (71%)</td>
</tr>
<tr>
<td>It is beneficial to have blood tests at home prior to outpatient clinic visit</td>
<td>11/15 (73%)</td>
<td>11/14 (79%)</td>
</tr>
<tr>
<td>Decisions about treatment changes were easier because of the timely availability of blood and stool test results</td>
<td>14/16 (88%)</td>
<td>9/14 (65%)</td>
</tr>
</tbody>
</table>

[Table1]

Conclusion: Enhanced nursing care service offered at home by out of hospital healthcare provider in collaboration with hospital IBD team was found to be very beneficial by both patients and parents.
Disclosure of interest: AM had received speaker fee and travel support from Abbvie. RM had received research grants, travel and educational support and speaker fee from Abbvie The enhanced nursing care service is funded by Abbvie, however Abbvie has no input into the development of this survey, analysis of the results and the preparation of this abstract.

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Objectives and Study: About one third of paediatric inflammatory bowel disease (IBD) patients have a surgical intervention in five years after diagnosis. The complication rates after bowel resection and colectomy are lower in surgical centres with greater experience, however, there is only very few prospective, epidemiological studies evaluating surgical management in pediatric IBD. Our aim was to evaluate the characteristics of surgical management in paediatric patients with IBD based on prospective, nation-wide inception cohort registry (HUPIR).

Method: Newly diagnosed paediatric patients with IBD (ages 0-18 years) has been registered in this prospective, nation-wide registry (HUPIR), and followed-up. The questionnaire at registration includes epidemiological data, disease extension, disease activity and initial therapy. The follow-up questionnaire consists of questions about disease activity and therapy (medication and surgery). Patients registered between 1st of January 2010 and 31 of December 2015, and had at least 1 year follow-up were involved to evaluate the surgical practice in Hungary. The urgency of the interventions, the experience of the surgeon and whether adult or paediatric surgeon performed the operation were analysed. Descriptive statistical methods were applied for data analysis.

Results: Between 2010 and 2015 827 children were registered (Crohn's disease (CD): 536, ulcerative colitis (UC): 237, IBD-U (unclassified):54). From the 827 patients 92 had surgical intervention (12%) (CD, 87, UC, 4,IBD-U,1). Surgical intervention due to perianal disease was in almost half of the CD patients (48%, 44/87). Bowel resection was performed in 36% of CD patients (33/87) and 5 patients had intraabdominal complications requiring surgical intervention. Interestingly, only 3 UC patients (2%) had colectomy (3/237). About one third (31%, 18/59) of the interventions were urgent surgical cases. Two-third of cases (63%, 34/54) was operated by paediatric surgeon. Ten years or more surgical experience were found in 78% (38/49).

Conclusion: Data of our prospective, nation-wide registry showed the frequency of surgical intervention in CD was similar to previous data, however, colectomy in UC was less common. The vast majority of surgical interventions were performed by paediatric surgeons.

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Multicenter study show a increase incidence of inflammatory bowel disease in a seven years period

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²Centro Hospitalar Médio Ave, Famalicão, Portugal
³Hospital de Santa Maria Maior, Barcelos, Portugal
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⁵Centro Hospitalar do Porto, Porto, Portugal
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⁷Pediatric Gastroenterology, Hepatology and Nutrition Unit, Clinical Academic Center (2CA), Hospital de Braga; Life and Health Sciences Research Institute (ICVS), ICVS/3B's-PT Government Associate Laboratory and School of Medicine, University of Minho, Braga, Portugal

Objectives and Study: To determine the incidence in pediatric population of Inflammatory bowel disease (IBD) in a 1200000 inhabitants region of Europe, characterize the inaugural episode; compare the results with first incidence of IBD in a Portuguese population in a previous prospective study conducted in the same region during a 12 months period (1May08 up to 30April09), IBD incidence 4.2 (1.5 Ulcerative colitis(UC);2.7 Crohn disease(CD)/100000) under 18 years(y).

Method: Prospective study from 1December2016 to 30November2017 in a tertiary hospital, confirmation of all cases by a multicenter retrospective study. During this period all new diagnosed cases of IBD with an age up to 18 years living in this region were reported (the all 5 public Hospital of the region, a pediatric gastro unit in Porto) and a questionnaire was filled up. Data from Census were used to calculate the incidence. Incidence was compared with previous results in the same region.

Results: During this period there were 23 new diagnosed cases of IBD(15CD, 7UC and 1 indeterminate colitis), 61%males. Median age 14.0 y (8-17 y); CD 13.7(8-17y), UC 14(12-17y). The presentation symptoms were abdominal pain in 20(7/7 UC), diarrhea in 16(7/7 UC), rectal bleeding in 16(7/7 UC), 8 had weight loss(3/7UC); 3 had fever(1/7UC); 2 had perianal abscess(0/7 UC) and one arthritis. The symptoms had a mean duration of 3.7 (standard deviation (SD) ± 4.7 months) prior to diagnosis(UC 1.1±SD 0.4 m; DC 4.8 ±SD 5.4 m). Ten (43%) cases were diagnosed during summer months (july-september), while in winter 3 cases were reported. The diagnostic workup reveal anemia (hemog&LT; 11.5 g/dl) in 7(17 UC), elevated erythrocyte sedimentation rate (ESR>20 mm/h) in 7 (n=18; 2/6 UC), elevated C-reactive protein (CRP >2.9 mg/L) in 16 (n=18, 5/5 UC), elevated fecal calprotectin (>100 ug/ml) in all(n=18) and low ferritin (< 20 ng/ml) in 7(n=18; 1/5 UC). Upper endoscopy normal in 15(5/7 UC), the most frequent finding was erythematous gastritis(6), 1 had reflux esophagitis and 1 an esophageal perforation associated with eosinophilic esophagitis. Colonoscopy reveal pancolitis in 6/7 UC and 13/15 CD; incomplete colonoscopy in one CD with a severe stenosis distant to hepatic flexure; five had macroscopic stenosis, cobblestoning, and linear ulcerations in the ileum. Eight (53%) DC patients were treated in exclusive enteral nutrition in association with azathioprine(aza). Six started prednisolone with aza. All the patients with UC were treated with messalazine, associate with prednisolone in 5. During this time period 9 were treated with Anti-TNF therapy(3/7 UC), 8 with infliximab and 1 adalimumab.

The calculated incidence in this time period was 6.8 IBD/100000, with 4,4 DC and 2,1 UC (per 100000).

Conclusion: This study show an increased incidence of IBD, with more DC cases compared with UC as expected, but with increased UC incidence. It is interesting to see that about half of the diagnosis were in summer months raising the question about factors responsible to trigger the symptoms. Although the majority had signs of inflammation in analysis, a few add normal results in spite having active disease on colonoscopy. The exception is fecal calprotectin elevated in all the cases supporting the role of this exam in initial evaluation of the patients presenting clinical suspicion of IBD.

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Skin manifestations in Paediatric Inflammatory Bowel Disease (PIBD) patients on monoclonal therapy

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¹Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

Objectives and Study: Skin lesions in paediatric inflammatory bowel disease (PIBD) can occur as extra-intestinal manifestations of inflammatory bowel disease (IBD), with an averagely reported incidence of 15%. However, skin lesions can also be triggered by monoclonal therapy, although the mechanism of action remains uncertain. Monoclonal-related skin lesions in paediatric patients are little known and under-reported in literature. We describe skin changes after commencement of anti-tumour necrosis factor (anti-TNF) in PIBD patients from a single paediatric centre.

Method: A retrospective review of medical records from PIBD patients who developed skin lesions whilst on monoclonal between 2013 and 2017. Infliximab and Adalimumab were the anti-TNF medications evaluated in this study. Furthermore, patients referred for dermatology opinion were also analysed. Minor local cutaneous manifestations at injection site were excluded.

Results: 22 out of 690 (3.2%) PIBD patients were referred for dermatology opinion. 12 of the 22 (54.5%) had Crohn's disease, 7 of the 22 (31.8%) had ulcerative colitis and 3 of the 22 (13.6%) had IBD-unclassified (IBD-U). 11 patients were on Infliximab and 11 patients on Adalimumab. Females were twice frequently affected, age ranged from 6.4 to 17 years (mean of 12.7 years).

Four groups were identified:

- **Group A**: 10/22 (45.5%) were patients with skin lesions highly likely to be secondary to monoclonal treatment. 4 of the 10 were Infliximab-related and 6 of the 10 were Adalimumab-related.
- **Group B**: 5/22 (22.7%) were patients whose lesions were secondary to the disease. For example, one patient developed granulomatous formation on penile shaft, which was thought to be secondary to Crohn's and subsequently confirmed on skin biopsy.
- **Group C**: 4/22 (18.2%) were patients with incidental findings such as acne, hypopigmentation and epidermolytic palmoplantar keratoderma
- **Group D**: 3/22 (13.6%) were patients whose lesions were thought to be a combination of groups A, B and C such as eczema.

7 out of the total 22 patients (31.8%) needed skin biopsies in order to clarify the diagnosis. No cases of malignancy or cutaneous infections were reported. Mean latency for developing monoclonal-related lesions (Group A) was 1.6 years (range 0.4-3.3 years). In this group, monoclonal were maintained in all cases and lesions were treated topically. Clinical features of patients with monoclonal-related lesions are depicted in Figure 1.
Conclusion: Skin lesions in PIBD patients receiving monoclonal were considered to be drug-related in almost half of the cases. Psoriasis and psoriasiform lesions were seen with Infliximab. However, no pattern could be identified for Adalimumab-related skin lesions. Prompt referral for dermatology assessment in PIBD patients receiving monoclonal is advised.

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Colectomy-free survival and factors associated with it in children with ulcerative colitis managed in a tertiary IBD centre in the UK

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¹Birmingham Children's Hospital, Birmingham, United Kingdom

Objectives and Study: Colectomy-free survival is an important outcome for children with ulcerative colitis. There is only limited data available about long term outcome of children with ulcerative colitis. The aim of our project is to review the outcome of colectomy-free survival and associated factors in patients with ulcerative colitis managed in our centre.

Method: We performed a retrospective analysis of all patients diagnosed with ulcerative colitis in our hospital from January 2010 to December 2015. The patients were identified from the medical database of the paediatric gastroenterology unit and paediatric surgical unit. The clinical, laboratory, endoscopy data and medical and surgical treatment were analysed.

Results: 147 patients with ulcerative colitis were identified in the study period, 85 (58%) were male patients. The median age at diagnosis was 12.9 years (2.2 to 17 years) and median duration of follow up was 34 months (12 to 96 months). 105 (72%) recorded pancolitis (E4) at diagnosis while 26 (18%) and 15 (10%) had extensive (E3) and left sided (E2) lesions respectively. Severity of disease at diagnosis, documented as physician global assessment, was mild in 50 (34%), moderate 70 (48%) and severe in 26 (18%) patients. 55 (37%) patients had no relapse in first year after diagnosis. 90 (61%) patients were in clinical remission at both 3 months and 12 months after diagnosis. 86 (59%), 54 (37%) and 46 (31%) patients received steroid treatment at diagnosis, 3 months and 12 months after diagnosis respectively. 145 (99%) patients received treatment with Mesalazine during the follow-up period. 93 (63%) patients were treated with Azathioprine and 66% of these patients were commenced on Azathioprine treatment within 6 months of diagnosis. 31 (21%) patients received treatment with Infliximab and median time to start Infliximab was 1.4 years (3 months to 7 years). 12 (8%) patients had surgery (sub-total colectomy) and chronic active severe UC was the indication for surgery in all patients. Factors associated with colectomy were steroid treatment at 3 months after diagnosis (75% v 34% p value 0.05), steroid treatment at 12 months after diagnosis (92% v 28% p value 0.01) and longer time interval from diagnosis to initiation of Infliximab treatment (10.4 months v 19.8 months p value 0.01). Age, extent and severity at diagnosis, the laboratory parameters at diagnosis including Hb, ESR, CRP, albumin, platelets, number of relapses in first year after diagnosis, number of episodes of hospitalisation for intravenous steroids and need for treatment with Azathioprine or Infliximab were not associated with colectomy.

Conclusion: Only a small proportion (8%) children needed colectomy in our cohort of patients with UC and the need for steroid use at 3 months and 12 months after diagnosis and longer interval to start treatment with Infliximab were associated with colectomy.

Disclosure of interest: RM had received research grants from Abbvie, Janssen & 4D Pharma, educational grants from Abbvie, Tillotts pharma and Dr Falk and speaker fee and honorarium for advisory boards from Abbvie, Pfizer and Dr Falk

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Chronic Recurrent Multifocal Osteomyelitis as extraintestinal manifestation of Inflammatory Bowel Disease. Experience of two paediatric tertiary referral centres

Daniela Knafelz1, Antonella Insalaco1, Fiammetta Bracci1, Bronislava Papadatou1, Sabrina Cardile1, Tommaso Alterio1, Sandrine Lacassagne2, Fevronia Kiparissi2

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2Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

Objectives and Study: Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare chronic inflammatory condition characterized by multifocal aseptic inflammation of bones, commonly metaphysis but lesions can occur anywhere in the skeleton. It can be associated with other inflammatory diseases and few cases reports have associated it with Inflammatory Bowel Disease (IBD). Aim of our study was to describe the experience of two tertiary paediatric IBD centres of CRMO and IBD.

Method: All the IBD patients treated in the two centres between 2012 and 2017 were retrospectively reviewed and those with CRMO were identified. Diagnosis of IBD was based on clinical endoscopic and histological results; diagnosis of CRMO was based on symptoms and whole body MRI results.

Results: Six patients with CRMO and IBD were identified over a total of 450 IBD patients followed in the two centres (1.3%); 2 males (M), 4 females (F); age range 7-17 years; 3 patients had Crohn's Disease (CD), 3 Ulcerative Colitis (UC). 3/6 (1 F; 2 M) presented with lower limb pain and raised inflammatory markers and were diagnosed having CRMO and were initially treated unsuccessfully with non-steroidal anti-inflammatory drugs (NSAIDs); subsequently developed bloody diarrhoea and abdominal pain associated with raised faecal calprotectin (respectively 6, 11 and 12 months after CRMO diagnosis). They underwent upper and lower GI endoscopy and were diagnosed with IBD (2 UC, 1 CD).

1/6 (F) presented with abdominal pain, fever and diffuse bone pain; upper and lower gastrointestinal endoscopy and biopsies were diagnostic of UC and whole body MRI of CRMO. The last two patients (2 F) presented with typical symptoms of IBD and were diagnosed with CD based on endoscopic, radiological and histological findings, they were initially treated with exclusive enteral nutrition (EEN) and whilst on treatment, they both developed lower limb pain and were diagnosed with CRMO after typical results on whole body MRI.

5/6 patients after the diagnosis of IBD and CRMO were treated with anti TNF alfa antibodies, 3 with infliximab (IFX), 2 with adalimumab (ADA), one refused treatment and her diseases are poorly controlled with NSAIDs and EEN. All patients treated with IFX and ADA went into and maintained remission of both IBD and CRMO.

Conclusion: CRMO can be considered a rare and poorly described extraintestinal manifestation of IBD. It may present before or after the onset of IBD. Our experience shows that once the underlying IBD is appropriately treated the CRMO also resolves.

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Objectives and Study: Research has shown clear correlation between chronic inflammatory conditions and a prothrombotic state. Central vein thrombosis is a severe complication in patients with inflammatory bowel disease (IBD), can cause non-specific and variable symptoms and hence lead to delays in diagnosis. We report the case of a 15 year old adolescent with IBD-U, who developed an extensive cerebral sinus vein thrombosis requiring placement of a ventriculoperitoneal shunt. Initial diagnosis was delayed due to the focus on severe colitic symptoms, with headache thought to be a consequence of active disease. An extensive review of the literature was carried out to document the prevalence of sinus vein thrombosis in children with IBD, to help clarify the current position on thromboprophylaxis in children with IBD.


Results: In our patient, the sinus vein thrombosis could have been due to active inflammatory bowel disease, dehydration, potential additional underlying thrombophilia, or a combination of all three. Search with “inflammatory bowel disease AND central vein thrombosis” revealed 18 results, mainly case reports. Amongst these was 1 retrospective study with prevalence of thrombotic events in 68,394 hospitalised children with IBD, showing an incidence of 117.9/10,000. The search for “Crohn's disease AND central vein thrombosis” and “ulcerative colitis AND central vein thrombosis” revealed 7 & 8 results respectively, predominantly case reports with retinal vein occlusion. The search for “inflammatory bowel disease AND central vein thrombosis AND children” revealed 1 case report of acute disseminated encephalomyelitis in conjunction with IBD. The search for “inflammatory bowel disease AND sinus vein thrombosis AND children”, “inflammatory bowel disease AND sinus vein thrombosis AND children AND thromboprophylaxis” and “inflammatory bowel disease AND thromboprophylaxis” revealed 0 results. Thus central vein thrombosis is reported as a rare complication of IBD in children. There is no published, evidence-based recommendation for thromboprophylaxis in children with IBD.

Conclusion: This case report highlights the need for clinicians to maintain vigilance for rare and unexpected complications of chronic disease. Signs and symptoms that do not easily fit with those of the primary condition must be reviewed with caution, and less common differentials excluded. Children with active IBD are in a prothrombotic state, and thus at an above average risk of thromboembolic events. As practice and guidance for thromboprophylaxis varies widely in paediatric IBD units, it would helpful for ESPGHAN to provide a position statement on thromboprophylaxis for children with IBD.

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Objectives and Study: Cyclosporin A is a second line drug in ulcerative colitis that failed to respond to intravenous glucocorticoids according to ECCO/ESPGHAN consensus. Up to date CsA induced mucosal healing (Mayo 0 score) is the only factor predicting the lack of course deterioration in the future. The aim of the study was to investigate a presence of factors contributing to positive CsA therapy outcome.

Method: It is a retrospective, single center study. We describe a clinical characteristic of 59 children (33F, 26M), mean age of 13.7 years, mean disease duration 32 months, who underwent CsA treatment in the course of UC in years 2005-2015. The primary endpoint was clinical remission (defined as PUCAI< 10) or clinical response (defined as decrease in PUCAI scoring for at least 20 points) at Day 8. Response/remission at Day 8 was achieved in 43 out of 59 (81%) and 31 out of 59 (58%) patients respectively. Clinical (PUCAI score), laboratory (CsA concentration), endoscopic (disease extension and severity) and demographic (age, age of onset, disease duration) data were used as independent variables in analysis of discrimination between: group with clinical response vs. no response and group with clinical remission vs. no remission.

Results: PUCAI score, UC duration and Mayo score create the model which predict clinical remission at Day 8 with sensitivity 0.8 and specificity 0.66. No model was established to discriminate between groups with clinical response vs. no response.

Conclusion: PUCAI score, UC duration and Mayo score contribute to response for induction therapy with CsA in children with UC.
Health related behavior in paediatric inflammatory bowel disease

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Objectives and Study: People with chronic disease are expected to be more responsible to their health related behavior as they go through their adolescent phase towards the adulthood. We assessed the general health and nutritional status of the adolescents with inflammatory bowel disease (IBD), and compared them with the general population (GP) of the same age through the national survey question.

Method: Cross-sectional study was done for sixty-two IBD patients followed at Severance Children's Hospital from July 2017 to October 2017. Confidential voluntary surveys selected from the Korea National Health and Nutrition Examination Survey (KNHANES) were administered to all IBD patients who agreed to participate in the study from age 9 to 19. Questionnaire items were thoroughly chosen by the IBD doctor, and selected seven categories thought to show differences between the IBD patients and GP are as follows: general well-being (hospital experiences or school absence), body image (self-body image and anthropometric data, body weight changes and efforts to reduce or maintain the body weight if any), sleeping, resting, stress, exercise, and eating habits. The results were compared with the data of the GP provided by KNHANES, which is open for public.

Results: Overall, there were significant differences between the IBD and the GP in days of school absences, hospitalization, and hospital visits (P = 0.0205, &LT; 0.001, and &LT; 0.001, respectively). Similar to GP, IBD patients regarded their weight as relatively average (40.98% vs 42.77%). Unlike GP, IBD tended to gain more weight than lose it when they tried to manipulate. They did not show differences in duration of sleeping or resting, degree of stress, and duration or intensity of the exercise. Although IBD tended to skip their lunch than the GP (P = 0.0082), number of eating out was significantly lower in IBD (P &LT; 0.001). We have subdivided the IBD group according to the age-under 13, 13 to 16, and 16 to 19. First group, defined to be pre-adolescent, did not show significant differences other than sickness and frequency of eating outs. Other groups also showed significant differences in sickness and eating outs, but they also tended to try to manipulate their weight towards gaining when GP of the same age group tried to lose it. None of the groups showed differences in the duration of sleeping or resting, intensity of exercise, and degree of stress. In assessment of the data within IBD patients by sex, there were significant differences in their efforts to manipulate their weight. Both the males and females were in the same trend in the weight change, but females tended to put effort to lose their weights (44%) when males did not put any effort to change one (41.67%). When we compared our data by the diagnosis, patients with ulcerative colitis tended to get more stressed out than patients with Crohn's disease (P = 0.006).

Conclusion: IBD adolescents tend to manage their health related behavior compared to the GP better, probably because of their frequent medical needs. However, since it can be different between the gender and the subclass of the disease, focusing on their degree of self-management about health related behavior may help the patients to control themselves better and moving onto the adult healthcare.

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Therapeutic approaches for perianal fistula in paediatric and adolescent onset Crohn’s disease - a multicentre cohort study

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Objectives and Study: There is no clear consensus on the management of Crohn’s disease related perianal fistulae (CD-PAF) in paediatric and adolescent onset CD due to paucity of data on management approaches. We aimed to evaluate therapeutic interventions and their efficacy in a multicentre cohort with paediatric and adolescent onset CD-PAF

Methods: Patients with paediatric and adolescent onset CD-PAF diagnosed since 2010 and having follow up data of at least 6 months since onset of CD-PAF were included. Patients with non-fistulizing perianal CD and those with rectovaginal or rectovesical fistula were excluded. Data were collected on demographics, clinical variables, pelvic MRI and surgical interventions. Complete clinical fistula healing was defined as the absence of any draining fistulas on clinical examination. Reinterventions were defined as the need for repeat abscess drainage, seton reinsertion, diverting stoma or proctectomy. Univariate and multivariate analysis was done for predictors of fistula healing and reintervention.

Results: 116 patients were included (74 boys and 42 girls). The mean age at diagnosis of fistula was 12.8 years. MRI was done in 85 of the patients with complex fistula in 57 (67%). Proctitis was evident at presentation in 33%. 55% had an abscess drainage but only 17 having a seton inserted. After onset of CD-PAF there was significant increase in the use of biologics (13.7% before and 83% after) and immunosuppressant (29% before and 80% after). Antibiotics were used 67% of the patients with median number of courses being 4 (range 1-8). Clinical fistula healing data was available in 78 patients of which 55 had complete and 18 had partial healing. There was significant difference in healing based on type of fistula (simple fistula 78%, complex fistula 26%, p=0.001). Follow up MRI scan (n=40) demonstrated partial healing in 29 and but complete healing in only 6 patients. Anti TNFs were continued in majority (86) of the patients. In the 10 patients stopping anti TNFs (6 - planned withdrawal, 4 - patient preference), 7 had recurrence of perianal fistula. Repeat surgical intervention was required only in 16% of the patients (repeat EUA and abscess drainage-9, diverting stoma-3 and reinsertion of seton-2). Complex fistula type (p=0.015), those with proctitis (p=0.04) and those needing abscess drainage (p=0.02) were more likely to need reintervention and patients with anti TNF therapy (0.01) less likely to need repeat surgery.

Conclusion: Perianal fistula in paediatric onset CD is managed with combined medical and surgical management in majority of patients. Significant proportion of patients had complete or partial clinical healing. Repeat surgical intervention in CD-PAF is only required in 16% of the patients.

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The role of thiopurine metabolite monitoring in the management of paediatric inflammatory bowel disease. A retrospective study done in Royal Aberdeen Children Hospital, Scotland

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Objectives and Study: Thiopurines has been proven to be effective in the treatment of inflammatory bowel disease (IBD). However, the use of thiopurines was often limited by its narrow toxicity profile and the difficulty with predicting individual patient response. Measuring the concentration of 6-thioguanine nucleotides and 6-methylmercaptopurine nucleotides produced by thiopurines had been proposed as a strategy to identify patient variations in drug response and toxicity.

Thiopurine metabolites monitoring was introduced into the Royal Aberdeen Children Hospital (RACH) in 2014 about three years ago. The service of providing metabolite monitoring test in RACH was reviewed. The indications and outcomes of thiopurine monitoring was evaluated. This study aim to investigate the indications for performing thiopurine metabolite testing, the clinical actions taken in accordance to the metabolite concentration and in which situation metabolite measurements could lead to a change in management.

Method: Patients with inflammatory bowel disease who were on thiopurine medication for at least eight weeks and had metabolite bloods taken between January 2014 and February 2017 were recruited. Hospital records were reviewed.

Results: A total of 37 patients were included. 70 metabolite samples were performed on these patients. All the metabolite samples were grouped into 51 episodes based on the reason for checking metabolite levels. The most common reason for performing metabolite test in RACH was routine measurement (43%), active disease (41.0%), adverse effects (7.9%), drug adherence assessment (5.9%) and a combined indication of flare + adverse effect (2.0%). The clinical actions taken in accordance to metabolite concentration include dose optimization (48.7%), further investigation (18.4%), education about compliance (9.2%), switch drug class (7.9%), add biologic (6.6%), cease drug (5.3%) and surgery (3.9%). An example was shown below.

Overall, metabolite testing lead to a change in management plan in 38 out of the 51 episodes (74.5%). Greatest rate of change was found in adverse effect and compliance groups (100% versus 100%), followed by active disease group (90.5%) and routine group (50.0%).

Conclusion: Metabolite testing led to a change in management in most cases especially in patients with toxicity and active disease. The most common change was dose change. The use of metabolite test to guide dose changes was useful particularly for patients with routine assessment and active disease. Prospective studies are needed to determine whether the use of metabolite testing to guide dose is of benefit. The clinical action taken in accordance to metabolite concentrations and the interval at repeating routine/repeat metabolite test in Royal Aberdeen Children Hospital should be standardized.

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The Sicilian Pediatric Network for Inflammatory Bowel Disease (SN-IBD): efficacy of biologics in Early-Onset IBD

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Objectives and Study: Early onset pediatric IBD (Eo-IBD) occurs in children ≤5 years of age with different outcome versus late-onset IBD. In the last few years, an increasing body of evidence is suggesting that children aged 0-6 years represent a distinct group of pediatric IBD patients in the pathogenesis, phenotype and therapy response. It has been reported that Eo-IBD is more resistant to standard and immunomodulatory therapies.

Method: A retrospective analysis was performed from the Sicilian Registry for IBD and included Eo-IBD treated with biologics. Infliximab (IFX) and adalimumab (ADA) were evaluated for efficacy in inducing remission.

Results: Six (n=6) patients, (F/M=4/2), with a mean age of 3.16 years (2-6 years) at diagnosis, received biologics. Ulcerative colitis (UC) and indeterminate colitis (IC) were more prevalent in our cohort, affecting respectively 3 and 2 children. Only one patient presented with Crohn's disease (CD). Children underwent biologic therapy consisting of IFX or ADA. In 2 patients, both drugs were used sequentially. Among n=8 treatments considered, the indication for biologic therapy was: n=1 (12.5%) steroid dependency, n= 3 (37.5%) active chronic disease; n=4 (50%) rescue therapy. Four were treated with ADA (2 for UC, 1 for CD, 1 for IC). Two (n=2; 50%) experienced prompt clinical remission at week 12 and 52, and mucosal healing was documented in one patient (n=1) at 52 weeks. Two patients (n=2, 50%) discontinued therapy for no-response after 2nd infusion. IFX therapy was administered in 4 patients (3 with UC, 1 with IC). Clinical remission was documented at 12 weeks follow-up in three (n=3; 75%) patients who received IFX, and only one patient experienced long term remission at 52 weeks. IFX was ineffective in one patient (n=1; 25%) and was discontinued.

Conclusion: Although it is generally accepted that many early onset IBD children have low response rates to biologics, in our cohort of pediatric early onset IBD, biologics were effective in 62.5% (5/8) of children in inducing response and remission. IFX provided better results compared to ADA. Our data showed relevant clinical benefit considering the higher rate of therapy failures reported in Eo-IBD.

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**Objectives and Study:** Biologics have been increasingly used to induce and maintain remission in pediatric inflammatory bowel disease (pIBD). The aim of this study was to describe real world experience with biologics in a pediatric Sicilian population with IBD.

**Method:** A retrospective, observational study was performed and the data were extracted from the IBD Sicilian Registry on children aged 6-17 years. Age, gender, Crohn's Disease (CD)/ulcerative colitis (UC) phenotypes, as well as indications for biologic therapy and clinical scores, were collected. Patients were classified regarding IBD type (CD/UC), and infliximab (IFX), adalimumab (ADA), and golimumab (GOL) therapies. Clinical response and remission were evaluated at 26, 52 and 104 weeks.

**Results:** Eighty-seven (n=87) patients received biologics for IBD from 2010 to 2017. The median ages at biologic start was 15.1 years. CD/UC prevalence was 63/24 (72.4%/27.6%). Indications for biologic therapies were: n= 28 (32.2%) steroid dependency; n=31 (35.6%) chronic active disease; n=19 (21.8%) steroid resistance; n=5 (5.7%) extraintestinal manifestations; n=1 (1.1%) adverse reactions to standard therapy and n=3 (3.4%) rescue therapy. Furthermore, n=18 patients (20.68%) received sequential biologics. The final statistical analysis focused on 101 treatments (CD n=74; UC n=27), with minimum follow-up of 26 weeks. In the CD group, at 26 weeks, 38 IFX total treatments showed disease remission in n= 23 (60.5%) and clinical benefit (PCDAI< 10) in n = 32 (84.2%). At 52 weeks, among 30 treatments completed, remission and clinical benefit were achieved in n = 22 (73.3%) and n = 28 (93.3%), respectively. At 104 weeks, out of 24 treatments evaluated, remission and clinical benefit were reported in 54.1 % (n=13) and 66.6 % (n=16) respectively. N=36 CD cases treated with ADA, showed, at 26 weeks, disease remission in 69.4 % (n=25), and clinical benefits in 88.9% (n=32). At 52 weeks, n =32 treatments maintained remission in n = 23 (71.8 %) and clinical benefit in n =27 (84.3 %). At 104 weeks, among 23 cases, remission in n=13 (56.5%) and clinical benefit in n= 15 (65.2 %), were observed. The UC cohort was evaluated for 21 cases in the IFX subgroup, with a remission rate at 26 weeks of 47.6% (n=10) and clinical benefit of 85.7 % (n=18). IFX evaluated in 12 cases at 52 weeks, was effective in achieving remission in n=8 (66.7 %), and clinical benefit in n=10 (83.3 %). At 104 weeks, disease remission and clinical benefit was stable in n= 4 (50%). Regarding n=5 ADA cases, 40% (n=2) had remission and clinical benefit at 26 weeks. Among n=4 cases considered at 52 weeks, remission and clinical benefit were stable in 50%. At 104 weeks follow-up, n=1 (33.3%) out of 3 treatments considered, was effective. Only one patient received Golimumab and showed remission both at 26 and 52 weeks.

**Conclusion:** In this cohort of Sicilian IBD children, biologics were effective in short and long-term disease with a percentage of response and remission superior to that seen in other studies. The results in CD patients were better than in CU patients.
### Efficacy of biologics in pediatric IBD

<table>
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<tr>
<th>Time</th>
<th>26 Weeks</th>
<th>52 Weeks</th>
<th>104 Weeks</th>
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<td><strong>CD-IFX</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
</tr>
<tr>
<td></td>
<td>23 - 60.50%</td>
<td>23 - 60.50%</td>
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</tr>
<tr>
<td><strong>CD-ADA</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
</tr>
<tr>
<td></td>
<td>25 - 69.40%</td>
<td>32 - 88.90%</td>
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<tr>
<td><strong>CD-GOL</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>UC-IFX</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
</tr>
<tr>
<td></td>
<td>10 - 47.6%</td>
<td>18 - 85.7%</td>
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<tr>
<td><strong>UC-ADA</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
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<td><strong>UC-GOL</strong></td>
<td>Remission n - %</td>
<td>Clinical benefit (remission+response) n - %</td>
<td>Total n</td>
</tr>
<tr>
<td></td>
<td>1 - 100%</td>
<td>1 - 100%</td>
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</table>

Contact e-mail address: claudia.romeo87@gmail.com
The Sicilian Network for Inflammatory Bowel Disease (SN-IBD): safety of biologics in pediatric IBD

Anna Claudia Romeo¹, Valeria Dipasquale¹, Salvatore Accomando², Paola Alga², Alessandra Tricarico², Marco Ventimiglia³, Michele Citrano³, Lucrezia Bruno³, Francesco Graziano³, Ambrogio Orlando³, Mario Cottone³, Claudio Romano³

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Objectives and Study: The incidence of pediatric inflammatory bowel disease (IBD) has risen over the several decades and therapeutic strategies continue to evolve. Biologic agents have been used to treat pediatric IBD for many decades. The aim of this study was to evaluate the safety of, and adverse events (AE) associated with, biological therapies in a cohort of a pediatric population.

Method: the data were obtained from the Sicilian Pediatric IBD Registry with a retrospective observational study in children with IBD ≤16 years of age. We assessed the safety of biologics in 87 children, aged 6-17 years, with IBD.

Results: Eighty-seven (n=87) patients received biologics for IBD. Crohn's disease (CD) was the most common disease (n=63; 72 %), followed by n = 24 (27%) patients with ulcerative colitis (UC). N= 52 (59.8 %) of this cohort was male, n= 35 (40.2 %) female. N=18 patients received more than one biologic during the observational period, for a total of 108 treatments considered. N=43 (39 %) patients received adalimumab (ADA), n= 63 patients (58 %) received infliximab (IFX), 1 patient (0.9%) was treated with golimumab (GOL) and 1 patient with vedolizumab (0.9%). N=10 patients (15.87 %), treated with IFX, reported adverse events due to biologic therapy, and AE led to drug discontinuation in 8 children. AE occurred 8.87 months after therapy start (ranging from 2 to 35 months), and 5 patients reported AE in less than 6 months from biologic start. AE reported were: n= 2 chest pain and flushing, n=1 nausea and hypertension, n=1 chest tightness, n=1 headache, n=2 lipothymia, n=1 angioedema, n=1 laryngospasm, n=1 anaphylactic shock, n=1 dyspnea. Another patient, affected by Crohn's disease experienced varicella infection that required biologic discontinuation after 27 months of IFX therapy.

Conclusion: In this retrospective study, we reported 10 adverse events (11.49%), all associated with IFX, one of which was documented as major (anaphylaxis). One other patient interrupted therapy due to varicella infection, which occurred under IFX therapy. No adverse events related to other biologics considered were documented. Biologic therapy with IFX /ADA is generally well tolerated and safe, but awareness and careful monitoring of side effects and vaccine preventable illnessness are required.

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Soluble transferrin receptor/log ferritin index is the most efficient marker of iron deficiency in children with inflammatory bowel disease

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Objectives and Study: Iron deficiency is a significant problem in children with inflammatory bowel disease (IBD). It is a major cause of anaemia and may impair immune response, cognitive functions and physical development. Since most of widely applied markers of iron homeostasis are affected by inflammation, the recognition of iron deficiency in children with IBD consists on multiple-criteria approach. The aim of the study was to identify a reliable and independent on inflammation marker of iron deficiency in children with IBD.

Method: The study group comprised 75 children with IBD, including 46 (61%) with ulcerative colitis and 29 (39%) with Crohn's disease. All children underwent blood tests including complete blood count, iron, ferritin, transferrin and transferrin saturation (satTf), soluble transferrin receptor (sTfR), hepcidin, C-reactive protein, erythrocyte sedimentation rate and interleukin-6. The sTfR/log ferritin index was calculated as sTfR/log₁₀ ferritin. Iron deficiency was defined by the ferritin level < 30ng/ml in patients with IBD remission or satTf < 20% with ferritin < 100ng/ml in patients with active IBD. Correlations between iron indicators and inflammatory markers were expressed by the Spearman’s rank correlation coefficient. We compared sensitivity (SENS), specificity (SPEC), accuracy (ACC) and positive and negative predictive values (PPV and NPV) of sTfR, sTfR/log ferritin index, hepcidin and red blood cells indices (MCH, MCHC, RDW) at predicting iron deficiency in IBD children. The ability of diagnostic parameters to identify iron deficiency was examined by receiver operating characteristic (ROC) analysis. The study was approved by the local bioethical committee.

Results: In the study group iron deficiency was recognized in 50 (66.7%) children. Iron depletion was stated in 33 out of 46 (71.7%) patients with ulcerative colitis and 17 out of 29 (58.6%) with Crohn’s disease (p=0.24). Among analysed parameters solely sTfR/log ferritin index and hepcidin did not correlate with any inflammatory marker. Using optimized cut-off sTfR/log ferritin (>0.646) with ACC 88%, SENS 98%, SPEC 63%, PPV 83%, NPV 94% and sTfR (>1.022 µg/ml) with ACC 77%, SENS 82%, SPEC 67%, PPV 82% and NPV 67% best predicted iron deficiency. Hepcidin (< 11.552 ng/mL), MCH (< 29.1pg), RDW (>12.5%) and MCHC (34.3g/dL) were very sensitive markers (100%, 96%, 94%, 90% respectively), although their specificity was poor (25%, 32%, 32%, 44% respectively). The best diagnostic utility in the recognition of iron deficiency showed sTfR/log ferritin with area under ROC (AUROC) of 0.922 (SE: 0.031; 95%CI: 0.862-0.982), sTfR with AUROC 0.755 (SE: 0.061; 95%CI: 0.635-0.876) and MCH with AUROC 0.720 (SE: 0.062; 95%CI: 0.599-0.842). The area under ROC of other parameters was as follows: RDW 0.660 (SE: 0.068; 95%CI: 0.526-0.794), hepcidin 0.640 (SE: 0.070; 95%CI: 0.502-0.777), MCHC 0.637 (SE: 0.072; 0.496-0.778).

Conclusion: The sTfR/log ferritin index is independent on inflammation and superior to other indicators in detecting iron deficiency in paediatric patients with IBD. The use of sTfR/log ferritin index may improve the routine diagnostic anaemia work-up in IBD patients.

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The Sicilian Pediatric Network for Inflammatory Bowel Disease (SN-IBD): safety of biologics in Early-Onset IBD

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Objectives and Study: Inflammatory bowel disease (IBD) has increased considerably over the last 50 years, with 25% of cases which are childhood/adolescence onset. In children younger than 6 years a careful selection is required to differentiate conventional IBD from monogenic disorders with IBD like phenotype at onset, due to the more severe disease course and different clinical approach. Early onset pediatric IBD (Eo-IBD) requires more aggressive medical therapy with immunomodulators and biologics.

Method: A retrospective, comparative, descriptive analysis was performed in 6 patients with Eo-IBD to evaluate the safety of biologic therapies (Infliximab, IFX and Adalimumab, ADA).

Results: Six (n=6) patients, F/M=4/2, with a mean age of 3.16 yrs, received biologics (ADA, IFX), 3 patients with ulcerative colitis (UC), 1 with Crohn's disease (CD) and 2 patients with indeterminate colitis (IC). Two patients (33.3%) underwent sequential biologic treatment with IFX and ADA. A total of 8 biologic treatments were included in this study (n=4 IFX, n=4 ADA). No adverse events (AE) were reported in the ADA group. In the IFX Group, laryngospasm was reported in 1 patient, which occurred at the second infusion, and in 1 patient, psoriasis-like skin lesions were reported.

Conclusion: Our findings, in a small group of patients, showed an incidence of 25% of AE associated to biologic therapy. The adverse events, described in our pediatric early onset IBD cohort, both occurred during IFX treatment and required suspension of biologic therapy.

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**Gastroenterology - Inflammatory bowel disease**

**G-P-365**

**Diagnosis and features of debilitating phenotype: perianal fistulising Crohn’s disease**

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**Objectives and Study:** Perianal disease is a common manifestation of Crohn disease (CD) that results in significant morbidity, decreased quality of life, and predicts poor outcome. Despite limited data, the incidence of perianal Crohn's disease (pCD) has been estimated to be 8% to 24% in pediatric patients. However, rather low incidence of fistulising pCD in pediatric patients should be evaluated cautiously by taking the diagnostic accuracy and limitations of the imaging techniques into consideration. The aim of this study was to evaluate the children with fistulizing pCD from clinical, laboratory, and endoscopic point of view, and analyze the accuracy of perianal MRI in diagnosis.

**Method:** Children with Crohn's disease who were diagnosed ≤18 years of age and followed up at least one year were revised. Clinical, endoscopic, laboratory and radiologic data from 50 patients who underwent comprehensive evaluation were compiled. Perianal magnetic resonance imaging (MRI) technique was used in all patients who have suspicious perianal finding. Then, patients were stratified into groups according to the presence or absence of fistulising pCD in their perianal MRI.

**Results:** Of the 50 enrolled patients, the mean age was 13 ± 3.7 years and %58 were male. Fistulising disease was demonstrated by perianal MRI in all patients with suspicious perianal finding. Fistulising pCD was detected in 26 patients (52%), 19 (38%) had at admission and 7 (14%) developed during the course of disease. Perianal abscess coexisted in 6 of 26 (52%) patients with fistulising pCD. Age, anthropometric parameters, duration of symptoms before the diagnosis, disease location and behaviour were not different between fistulising and non-fistulising groups. However, patients with fistulising perianal disease had higher PCDAI score, platelet count and lower serum albumin level compared with those without perianal involvement (p&LT; 0.05). Seton placement (abscess drainage when necessary) was carried out in 12/26 patients by a surgeon specialized in inflammatory bowel disease surgery. Children with pCD at admission were treated with treated anti-TNFα as the first line therapy, and anti-TNFα was also added to the ongoing treatment in children who developed perianal disease during the follow-up.

**Conclusion:** The frequency of perianal involvement in pediatric patients is thought to be more common than it has been reported. Perianal MRI is a preferable radiologic technique that can contribute diagnosis of fistulising pCD and its potential complications. Thus, perianal MRI should be included into the baseline diagnostic evaluation in every child with Crohn's disease who has not a normal perianal examination. Prompt recognition of pCD may provide an appropriate therapeutic approaches and an improved quality of life.
GASTROENTEROLOGY - Inflammatory bowel disease

G-P-366

Current status of the transition from pediatric to the adult IBD care units in Spain: Differing perceptions of adult and paediatric gastroenterologists

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Background and aims: The orderly process termed transition is vital for successful follow-up of adolescents with IBD in the adult IBD units. The aims of our study were to establish the real situation of transition models in our country and to identify the perceived needs, requirements and barriers to successful transition from the perspective of pediatric and adults gastroenterologists involved in the process.

Methods: A structured survey designed for self-completion was distributed through the mailing lists of the Spanish Society for Pediatric Gastroenterology, Hepatology and Nutrition (SEGHNP) and of the Spanish Working Group on Crohn’s Disease and Ulcerative Colitis (GETECCU) comprising paediatric and adult gastroenterologist with an interest in IBD. The questionnaire contained closed questions as well as ranked items concerning current status of transition care in Spain, perceived needs for an effective transition in IBD, and the organisational, clinician and patient related barriers for a successful transition.

Results: A total of 138 answered surveys were received, 53 % from paediatricians and 47 % from adult gastroenterologists from 90 Spanish hospitals, 66 % tertiary centres. A higher response rate was achieved from paediatric gastroenterologists (19 %, 73/402) as opposed to adult gastroenterologist (9%, 65/803) (p=0.03). A structured transition programme is adequate established in 43 % of centres (53.4 % of paediatric versus 34 % of adult gastroenterologist, p &LT; 0.05) A structured transition service was perceived as very important by the 79.5% paediatricians compared to 63% of the adult gastroenterologists (p=0.03). A higher proportion of adult and paediatric gastroenterologists identified inadequacies in the preparation of adolescents for transfer (43% and 38%, p=ns). The main areas of perceived deficiencies were lack of knowledge of the patients about their illness and treatment, lack of self-advocacy and coordination of care. Lack of resources, time, and a critical mass of patients were the factors ranked highest by both groups as barriers to transition care. Both adult (54%) and paediatric gastroenterologists (55%) highlighted suboptimal training in adolescent medicine.

Conclusions: This survey highlights differences in the perception of adult and paediatric gastroenterologists in the management of transition care and perceived competencies for adolescents with IBD. In our country, less than a half of the centres have developed a structured transition programme. Lack of training, time and insufficient resources are the main barriers identified for development of a successful transition service.

Acknowledgments: To all the members of SEGHNP and GETECCU that participated with their surveys

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**GASTROENTEROLOGY - Inflammatory bowel disease**

G-P-367

**Deficiency of respiratory chain complexes in the intestinal epithelium in pediatric inflammatory bowel disease**

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**Objectives and Study:** The etiology of inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), is multifactorial. As the intestinal epithelium is a site harboring cells with a high energy demand, it seems evident that mitochondrial activity plays a role in the complex pathogenesis as well. The aim of the research project is to investigate if mitochondrial dysfunction and subsequently an energy deficiency in intestinal epithelial cells (IEC) is a pivotal component of the transmural inflammatory process in IBD.

**Methods:** Colonic mucosal biopsies of 5 pediatric patients with CD and UC at first diagnosis and 5 healthy individuals were obtained during a colonoscopy. Residual material from the terminal ileum, ascending colon and rectum was fixed in formalin, embedded in paraffin and cut. An immunohistochemical staining was done for complex I to V of the respiratory chain and the porin, a protein of the outer mitochondrial membrane protein using monoclonal mouse antibodies and following a standardized protocol. For evaluation a scoring system from 0-3 was used to quantify differences in staining intensity (0: no staining; 1: weak; 2: moderate; 3: strong). The staining intensities (MW I) were multiplied by the percentage of positive cells (MWE) to yield score values and the mean value of the results of two independent examiners was obtained.

**Results:** In these preliminary results 33 biopsy specimens of 5 patients of each group were stained and evaluated. Regarding complex I expression in the cells of the colonic crypts, the UC group showed a reduction of 33% and the CD group of 29%. In some samples even a complete loss was observed. Complex IV showed a significant reduction in the disease groups as well, even if the reduction was only 13% in the UC group, 16% in the CD group and no complete loss was observed. Complex II, III and V as well as porin showed no significant differences, the results can be seen in figure 1.
Conclusion: As complex I is involved in several apoptotic mechanisms, intestinal epithelial cells, lacking complex I, might provoke the immune system to cause chronic inflammation. A precise knowledge of the behavior of mitochondria in IEC is needed and might help to elucidate the pathogenesis of IBD.

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Cytokine tumour necrosis factor-alpha (TNF-α) a promoter gene polymorphism at position -308 G/A and relationship with complicated disease course in children with Crohn’s disease

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Objectives and Study: The aim of this study was to find out whether the presence of TNF-α 308 G/A polymorphism affects the course of Crohn’s disease (CD) and whether this polymorphism is a suitable predictor of a complicated course.

Method: The data of newly diagnosed CD patients < 19 years of age were prospectively collected from 1st September 2005 to 30th September 2017 in the computerized clinical database. We included only patients who meet the diagnostic criteria for CD and agreed to genetic examination. Genotyping was carried out with the PCR-RFLP method. The complicated course of the disease was defined as the need of biological treatment during the observed period. Fisher’s exact test was used for statistical evaluation.

Results: The genetic examination was performed in 88 children with CD. The median age at CD diagnosis was 14.5 years (2.7-17.9). In 21 (24%) patients TNF-α 308 G/A polymorphism was present. Patients were monitored throughout the entire period (2 months to 12 years). A complicated course of the disease was registered in 32 patients (36%), of which 9 had a polymorphism of 308 G/A. The relationship between the presence of the 308 G/A polymorphism and the complicated CD was not significant (p=0.18).

Conclusion: The presence of TNF-α 308 G/A polymorphism does not affect the complicated course of CD. Examination of this polymorphism is not suitable for prediction of complicated course of CD.

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Remsima® is cost effective and safe in managing paediatric inflammatory bowel disease: A prospective study

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Background and aims: Remsima®/CT-P13 the biosimilar of Remicade® has recently entered the European market. There is limited data available on its use in Inflammatory Bowel Disease (IBD) in children. In this study we aimed to prospectively investigate the safety and cost implications of 1) switching from Remicade® to Remsima® in children with IBD 2) Initiating treatment with Remsima in children with IBD.

Methods: All children who were treated with Remicade® for IBD in the Department of Paediatric Gastroenterology at The Royal London Hospital were switched to Remsima®. All children with IBD whose treatment required escalation to a biological were started on the biosimilar, Remsima® instead of Remicade®. Primary endpoints include a change in inflammatory markers, change in disease activity score, and the development of any adverse effects. The total number of infusions and their cost were recorded from January 2017 to November 2017. The C-reactive protein (CRP) and Erythrocyte Sedimentary Rate (ESR) was measured prior to infusion. Adverse effects were recorded in all patients immediately after infusion and reassessed at both virtual and face to face clinics post infusion.

Results: Our cohort consisted of 63 IBD children (34 male and 29 female) with a median age of 14 (range 7-16). 48 children with Crohns and 15 with UC. 45 (35 Crohns, 10UC) children were switched from Remicade® to Remsima®. 18 (13 Crohns, 5UC) children started treatment with Remsima® having never previously been on Remicade®. Median follow up was over 8 months (range of 1-9 months). 280 infusions have been performed since January 2017. 235 of these were Remsima® and 45 were Remicade®. The cost of a single vial of Remsima® 100mg vial is £162.00, 53.6% cheaper than Remicade® 100mg. The average infusion dose in this study was 350mg which equates to a cost saving of approximately £150,000 over 9 months. 84% of patients tolerated the medication without any adverse effects. 84% of patients had improved disease activity scores, which correlated to improved or normalised inflammatory markers. 9.5% of patients developed an adverse reaction to Remsima®. 4.8% of patients developed anaphylaxis to Remsima®, and less than 5% developed antibodies.

Conclusion: We demonstrated that switching from Remicade® to Remsima® was cost effective, safe and feasible. Switching was not associated with significant side effects and did not impact the short term clinical outcomes in children with IBD.

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Adalimumab monotherapy is as effective as combination therapy in paediatric Crohn's disease

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Objectives and Study: Adalimumab is an effective treatment for induction of remission and maintenance of remission in children with Crohn's disease (CD). The value of combination therapy with Adalimumab and immunosuppressive agents including Thiopurines and Methotrexate is unclear. The aim of this project is to compare the outcome of CD patients receiving Adalimumab monotherapy and combination therapy in real-life setting.

Method: We have done a retrospective review of the medical records of CD patients receiving Adalimumab treatment. The data was collected for a period ranging from January 2013 to August 2017. We collected data on patient demography, disease characteristics, co-immunosuppression, laboratory parameters, clinical remission (defined by Physician Global Assessment), mucosal healing (assessed by Simple Endoscopic Score-CD), serious side effects including malignancy and serious infections, Adalimumab drug levels and the need for dose/frequency adjustment of Adalimumab.

Results: 55 CD patients have received Adalimumab treatment. 17 patients were on monotherapy and 38 patients on combination therapy. Patient characteristics and disease characteristics were similar in both the groups. Thiopurines and Methotrexate were the co-immunosuppression in 33 (87%) and 5 (13%) patients respectively. There was no statistically significant difference between rate of clinical remission, mucosal healing, CRP normalisation, dose/frequency adjustment of Adalimumab. No serious infections or malignancies were recorded in patients in both the groups. Details in table 1

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab monotherapy N=17</th>
<th>Adalimumab Combination therapy N=38</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (range)</td>
<td>13 years (2.5-17)</td>
<td>12 years (6-15.5)</td>
<td>n.s</td>
</tr>
<tr>
<td>Disease distribution</td>
<td>L1 8 (47%) L2 2(12%) L3 7(41%)</td>
<td>L1 6(16%) L2 12 (32%) L3 20 (52%)</td>
<td>n.s</td>
</tr>
<tr>
<td>Indication for</td>
<td>16 (94%)</td>
<td>30 (79%)</td>
<td>n.s</td>
</tr>
<tr>
<td>Adalimumab treatment</td>
<td>Luminal CD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>24(8-40)</td>
<td>22(1-47)</td>
<td>n.s</td>
</tr>
<tr>
<td>Clinical remission at last</td>
<td>12 (71%)</td>
<td>28 (74%)</td>
<td>n.s</td>
</tr>
<tr>
<td>follow-up(PGA) Remission</td>
<td>5 (29%)</td>
<td>10 (26%)</td>
<td></td>
</tr>
<tr>
<td>Complete mucosal healing (SES-CD score 0)</td>
<td>6/10 (60%)</td>
<td>19/24 (79%)</td>
<td>n.s</td>
</tr>
<tr>
<td>% of patients needing</td>
<td>10 (59%)</td>
<td>16 (42%)</td>
<td>n.s</td>
</tr>
<tr>
<td>dose/frequency adjustment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab levels &lt;5</td>
<td>5/17 (25%)</td>
<td>10/17 (59%)</td>
<td>n.s</td>
</tr>
<tr>
<td>5-10 &gt;10</td>
<td>2/17 (12%)</td>
<td>19/31 (61%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/31 (35%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Table1]
Conclusion: Monotherapy with Adalimumab is as effective and safe as combination therapy in children with Crohn's disease.

Disclosure of interest: RM- Received research grants from Abbvie, Janssen & 4D pharma, educational grants from Abbvie, Dr Falk and Tillotts pharma and speaker fee/honorarium for advisory board from Abbvie, Pfizer and Dr Falk

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-371

Ultrasound parameters of bone density in children with inflammatory bowel disease (IBD) - a follow up study

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Objectives and Study: The aim of the study was to analyse the changes of quantitative ultrasound densitometry and bone turnover markers in children with IBD. The study also examined the effects of duration of the disease and steroid treatment on bone density.

Method: Participants included 58 children with IBD (36 girls, 22 boys); 38 patients with Crohn’s disease, 19 patients with ulcerative colitis (UC) and 1 patient with indeterminate colitis. Mean age was 13.5±2.6 years (range 5.5 to 17.5). The mean duration of the disease was 15.0±14.4 months. The mean time between two visits was 1.2±0.3 years. Total of 39 patients were treated with steroids at the beginning of the study. Calculation of cumulative steroid effect included scoring three variables; daily dosage, duration and mode of treatment (continuous or intermitent), (maximal score 5). Measurements of bone markers (osteocalcin, telopeptide and procollagen) were performed by standard methods. The right heel quantitative ultrasound included parameters: broadband ultrasound attenuation (BUA; dB/MHz), the speed of sound (SOS; m/s) and the quantitative ultrasound index (QUI;%). The Z-score s for BUA and SOS were calculated. The differences between multiple dependent groups were tested with analysis of variance (ANOVA) for repeated measurements and the level \( \alpha \) was set to 0.05.

Results: Osteocalcin, procollagen and telopeptide were increased according to the reference values for adults. Mean cumulative steroid effect score was 3.1 ± 2.3. Mean Z scores for SOS and BUA were -0.19 ±1.17 and -1.38±1.14, respectively. Significant increase in BUA (p &LT; 0.001), BUA Z score (p=0.036), SOS and QUI (p &LT; 0.001) was found between baseline and second measurement. Significant increase in osteocalcin (p=0.022) and pro collagen (p=0.044) and significant decrease in telopeptide (p=0.022) was found between two measurements. There were no significant differences in biochemical and ultrasound bone parameters between patients with UC and Crohn’s disease, in both measurements. No difference in biochemical or bone density results was found between patients who received steroid therapy in comparison to those without steroid treatment. Patients with disease duration ≥6 months had significantly lower baseline values of SOS (p=0.004), SOS Z score (p=0.002), BUA Z score (p=0.010) and QUI (p=0.018) than those with disease duration &LT; 6 months. In the second measurement, a significantly lower osteocalcin (p=0.015), BUA (p&LT; 0.001) and SOS Z score (p&LT; 0.001) were also observed in a group with disease duration ≥6 months.

Conclusion: Significant increase in ultrasound bone density parameters during follow-up period indicates that inflammatory bowel disease in children and adolescents did not significantly impair the bone mineralization even in patients treated with steroids, in those probably due to low cumulative steroid effect. However, children with longer duration of the disease had significantly lower ultrasound parameters, even though the length of the disease did not significantly affect the biochemical parameters.

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Increased risk of acute pancreatitis in patients with inflammatory bowel disease - a meta-analysis

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Objectives and Study: Patients with inflammatory bowel disease (IBD) are at a higher risk for developing acute pancreatitis (AP). The elevated risk for pancreatitis may be a result of an extraintestinal manifestation of IBD, as well as medications, gallstones, and genetic disorders. The extent of this risk is, however, not well established. The aim of the present study was assessing the exact risk for AP in patients with IBD with the help of a meta-analysis.

Method: A systematic search with complex search queries was performed in PubMed/MEDLINE, Embase, SCOPUS, Web of Science and Cochrane Library databases using filters for “English” and “human”. The database search was conducted on the 30th of October 2017, and was based on a PICO question (Patients: patients with an AP episode; Intervention/Exposure: IBD patients; Comparison: non-IBD patients; Outcome: odds ratio). Screening and selection of the studies was conducted independently by two investigators (B.T, and B.S). We excluded review articles, conference abstracts and case reports from our present study. The reference lists of obtained articles were also checked. Articles were eligible if they reported number of patients with AP separately for IBD and non-IBD patients. For binary outcomes, odds ratios (OR) and 95% confidence intervals (CI), and summary OR estimation were calculated. ORs were pooled using the random effects model with the DerSimonian-Laird estimation. A two-sided p value of < 0.05 was regarded as statistically significant. The meta-analysis was performed with Stata 11 SE (Stata Corp).

Results: Our systematic search resulted in a total of 5687 studies. After removing the duplications 2679 individual publications remained. Of these 649 were selected for the full-text assessment, and 22 publications were found eligible for analysis. Seven of the 22 publication were case-control studies (including 120 393 patients), that assessed the proportion of comorbid IBD within the group of patients with their first AP episode. Another 2 case-control (90597 person) and 13 cohort studies (46390 IBD patients) reported the events of AP among IBD patients. Three of the cohort studies have assessed the paediatric population including 5217 children.

Comorbid IBD is twice as likely to occur in patients having their first AP episodes (OR = 2.13 [CI: 1.96, 2.32], p&LT; 0.00001). Also, an AP episode is three times more likely to develop in patients with IBD (OR = 3.14 [CI: 2.65, 3.72], p&LT; 0.00001). From another point of view, an episode of AP has developed in 1.26% of the whole IBD population [CI: 1.01-1.52%; p&LT; 0.00001].

Conclusion: Our meta-analysis showed, that IBD triples the odds of developing AP, and approximately every 1 in 100 IBD patients will suffer an episode of AP. The aetiology, clinical behaviour and prognosis of AP in IBD is, however, not well explored, and only limited data is available regarding the paediatric population. Therefore, we are planning to organize a prospective, multicentre observational study to characterize AP in paediatric patients with IBD (APRICOT study --- Analysis of Pancreatitis Risk in paediatric patients with IBD: a Clinical Observational Trial).

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-373

The role of vitamin D and vitamin D receptor gene polymorphisms in the course of inflammatory bowel disease in children

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Objectives and Study: The ethiopathogenesis of inflammatory bowel disease (IBD) is still unclear. Many studies suggest genetic component that may influence the incidence and the severity of the disease. Additionally, it has been found that low level of serum vitamin D may have an impact on the clinical course of the disease due to its effect on immunological system.

Method: We aimed to investigate correlation between incidence of vitamin D receptor (VDR) gene polymorphisms (rs11568820, rs10735810, rs1544410, rs7975232 and rs731236, commonly described as Cdx2, FokI, Bsm, ApaI and TaqI, respectively) and vitamin D concentration and clinical course of the IBD (disease activity, extent of the intestinal lesions). Data were obtained from 62 patients with IBD (34 with Crohn’s disease, 27 with ulcerative colitis), aged 3 to 18 years, and compared with controls (N=47), aged 8 to 18 years.

Results: Although there was no difference in the incidence of individual genotypes between study groups (IBD, C) in all polymorphisms examined, we described significant increase in the chance of developing IBD for heterozygotes of Cdx2 (2.3-fold with p = 0.04, OR: 2.3, 95% CI 0.96-1.85) and BsmI (2.07-fold with p = 0.048, OR: 2.07, 95% CI 0.95-1.82) polymorphisms. Mean serum 25OHD level in IBD patients was significantly higher compared to controls (19.87 ng/ml vs 16.07 ng/ml; p=0.03).

A significant correlation was found between vitamin D level and TaqI in IBD (p=0.025) and CD (p=0.03) patients as well as with BsmI polymorphism in IBD (p=0.04) and CD (p=0.04) patients. A significant correlation was described between the degree of disease activity and genotypes for FokI polymorphism in UC patients (p = 0.027) and between the category of endoscopic lesions and genotypes for Cdx2 polymorphism also in UC patients (p = 0.046).

Conclusion: Vitamin D supplementation should be recommended in both children with inflammatory bowel disease and in healthy peers. The results suggesting correlation of VDR gene polymorphism with the chance of developing IBD and clinical course of the disease require further studies on a larger group of patients.
Usefulness of Metallothioneins in diagnostics and monitoring of Inflammatory Bowel Diseases - a preliminary study

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Objectives and Study: Despite the progress in diagnostics and treatment of Inflammatory Bowel Disease (IBD) the new markers useful in estimation of inflammation severity and differentiating Crohn’s Disease (CD) from Ulcerative Colitis (UC) are still needed. The potential role of Metallothioneins (MT) - I/II in IBD may be related to regulation of metal ions (Cu, Zn, Cd) homeostasis, modulation of the activation of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and neutralization of reactive oxygen species. The expression of MT has been studied in patients with CD and UC, however the results of the researchers are inconclusive.

The general aim of this study was to investigate the differences in the intestinal MT-I/II and Ki-67 expression in the groups of patients with IBD vs. patients without organic disease as well as patients with UC vs. patients with CD. Moreover, the relationship between fecal calprotectin concentration (FCC), serum CRP concentration and studied markers expression in consecutive parts of the intestine was also examined.

Method: The study group (mean age 13.8 years) consisted of 11 patients with IBD (55% with UC and 45% with CD, respectively) and 10 patients without organic diseases. All of patients underwent colonoscopy with biopsy taken from ileum, caecum, colon and rectum. The immunohistochemical method was used for the examination of MT-I/II (epithelial cells and inflammatory cell infiltration) as well as Ki-67 (epithelial cells, stroma and inflammatory cell infiltration) expression evaluated using specific scales: SCORE and semiquantitative immunoreactive score (IRS). Specific method were used for serum CRP concentration (Immunoassay) and FCC (ELISA kits) analyses. All patients or patients and their parents signed formal consent for participation in the study and the approval of the local Ethics Committee was obtained (PMMH-RI 59/2016).

Results: The expression of MT-I/II was observed in cytoplasm of epithelial and inflammatory cells whereas Ki-67 in nuclei of epithelial, stromal and inflammatory cells. Statistical analysis showed the significantly higher percentage of epithelial cells with positive Ki-67 expression in rectum in the group of patients with UC than in patients with CD (p=0.026). However, positive expression of MT-I/II epithelial IRS in caecum was increased in the group of patients with CD than UC (p=0.018). Moreover, in the group of IBD patients the positive correlation in the expression of colon Ki-67 epithelium SCORE vs. CRP serum concentration was observed (r=0.749, p&LT; 0.05). Our study confirmed also a negative correlations between MT-I/II epithelium IRS in rectum vs. FCC (r=-0.635, p&LT; 0.05). No statistical differences between expression of studied markers in IBD and control groups were found.

Conclusion: The results of the study showed high potential of MT usage in differentiating CD from UC. The further research on a large group is needed to confirm our preliminary results and indicate the dependence of studied markers on severity and duration of inflammation as well as treatment process.

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**Objectives and Study:** Pediatric patients affected by Crohn Disease (CD) have an increase risk for low catch-up growth and bone mineralization disorders, due to the chronic inflammation, the malnutrition, and the malabsorption of nutrients. Our aim was to investigate the impact of Exclusive Enteral Nutrition (EEN) on the nutritional status and bone mineral density (BMD) in a cohort of pediatric CD patients.

**Method:** CD newly diagnosed patients were prospectively enrolled. At the time of diagnosis (T0), after induction therapy at 8 weeks (T8), at 26 weeks (T26) and after 52 weeks (T52) from the diagnosis, a complete physical evaluation was performed together with blood vitamins measurements. The Fatty Free Mass (FFM) and the Resting Energy Expenditure (REE) were measured through the use of Bioelectrical Impedance (BIA). Moreover at T0, T26 and T52 a dual-energy X-ray (DXA) was performed to assess patients' BMD. The non-parametric Mann-Whitney test or a linear regression analysis were performed when needed.

**Results:** Eighteen consecutive CD pediatric patients were enrolled in the study. The median age at diagnosis was 13 years (range: 8-16). Fourteen out of 18 were male (77.8%). All patients started EEN as remission induction therapy. At T8 and persistently significant also at T26, there was a reduction of the activity score of disease (p<LT 0.001) and of some main inflammation parameters studied such as the erythrocyte sedimentation rate and platelet count (p<LT 0.001 and p<LT 0.001). There was also an improvement of the z-score for the weight, the height, the Body Mass Index (BMI) and the tricipital plica measurement (p<LT 0.001, p<LT 0.001, p<LT 0.001 and p=0.006, respectively). At the BIA analysis there was a significant increase of FFM (p<LT 0.001) and of REE (p<LT 0.007) compared to T0. Moreover, between T0 and T8 there was an improvement of 25OH vitamin D (p=0.005), vitamin A (p<LT 0.001), vitamin B12 (p=0.01), folate (p<LT 0.001) and copper (p=0.004) blood levels. In addition, between T8 and T26 there was also a growth speed rate increase (p=0.03). Only 8 patients (44.4%), out of 18, reached the maximum follow-up (T52) and at this time point there was also a significant increase of BMD values compared to T0 (p<LT 0.001). At T0, T8 and T26, FFM was directly related to patients' weight, height and REE (p<LT 0.001). Moreover, at T0 and T26, FFM was also directly correlated to BMD (p=0.02 and p=0.01).

**Conclusion:** EEN improves the nutritional status in CD children for a sustained period by increasing serum vitamin levels and restoring the patient physical state through an increase of weight, BMI, growth speed and tricipital plica measures. EEN also enhance the FFM and REE, leading to the improvement of the basal metabolism rate. Moreover, preliminary data shows that EEN improves bone mineral composition. Finally, in our cohort of patients, the FFM is also directly related to BMD. Even if further studies are needed, our data suggests that FFM measured by BIA could represent a potential safer and indirect measure of children bone metabolism.

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Long term safety and efficacy of single dose parenteral iron in children with inflammatory bowel disease (IBD) in one of the largest tertiary centres in North England

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Objectives and Study: Iron-deficiency anaemia is a common complication amongst children with inflammatory bowel disease (IBD) and it can have a significant impact on the quality of their lives. Although single-dose parenteral iron preparations are an easily available treatment for children, there are still concerns surrounding its adverse reactions. There are not many longitudinal studies showing its sustained efficacy and effects.

The primary aim of this study was to evaluate the safety, side effects and efficacy of IV iron maltoside 1000 (Monofer®) at 6 weeks, 3 months, 6 months and 1 year after treatment in children with IBD. The secondary aim was to identify any evidence of iron overload.

Method: A comprehensive search was performed using the hospital's IBD database to identify patients who have been given parenteral iron from 2012 to 2016. Primary indication, underlying diagnosis, dose of iron (mg), adverse reactions and laboratory values before and after treatment were among the parameters recorded. Dose calculations were based on the Ganzoni formula. Parenteral iron was used only if oral iron therapy was ineffective (< 20g/L rise in 3 months), not tolerated, not advisable (IBD unstable) or iron-deficiency anaemia with haemoglobin levels of < 100 g/L. Repeated measures ANOVA was conducted for statistical analysis.

Results: A total of 27 patients were identified using the database (female = 15, male = 12). The median age was 15 and median weight was 33.9 kg (range 12.4 kg to 63.0 kg). Repeated-measures ANOVA conducted on 27 patients showed that mean haemoglobin differed significantly between time points \[ F (4, 104) = 29.416, p < .001 \]. Normality checks were carried out and were approximately normally distributed. Post-hoc tests using the Bonferroni correction revealed that mean haemoglobin increased significantly by 6 weeks and remained stable thereafter \( p < .001 \).

Mean Haemoglobin Level

![Mean haemoglobin level against time with error bars representing standard error.]

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Only one patient had an acute type 1 allergic reaction but did not fulfil the criteria for anaphylaxis. Two patients had evidence of hair loss at 3 months post-infusion. This reversed in the first child with the use of biotin for 3 months and in the second child, the hair loss reversed with the stoppage of azathioprine. Hence, these are unlikely to be secondary to iron overload. None of the patients had evidence of dysmetabolic iron overload syndrome (DIOS). All children had normal LFTs and GGTs on follow up biochemistry with no evidence of diabetes, chronic fatigue or hepatosplenomegaly within the notes of their follow up consultations.

**Conclusion:** Parenteral iron appears to have sustained efficacy in the treatment of iron deficiency anaemia in children with IBD. Iron status increased significantly by 6 weeks and sustained till 1-year post-infusion. The immediate reaction rate was 3.7% and none of the remaining 26 patients had any long-term or short-term side effects including any evidence of DIOS.

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Gastroenterology - Inflammatory bowel disease

Prevalence and risk factors for anxiety and depressive symptoms in children, adolescents and young adults with inflammatory bowel disease

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Objectives and Study: Young patients with inflammatory bowel disease (IBD) are at risk for developing anxiety and depression with a 10-50% prevalence rate. This study aims to describe prevalence and severity of anxiety and depressive symptoms in a Dutch cohort of young IBD patients, and identifies demographic and clinical risk factors.

Method: IBD patients (n=374; 10-25y) participating in a randomised controlled trial (ClinicalTrials.gov:NCT02265588) were screened for anxiety, depression and quality of life using validated age-specific questionnaires. Patients with elevated scores for anxiety and/or depression received a psychiatric interview assessing severity. Demographic and clinical characteristics were retrieved from medical charts. Multiple logistic regression analysis was performed to identify risk factors for anxiety and/or depression.

Results: Patients (mean age 18.9 y, 44.1% male, Crohn’s disease 60.4%) had disease in remission (76%), or mild, moderate and severe disease activity in respectively 19.5%, 2.7% and 2.1%. Psychological symptoms were absent, mild or severe in 52.4%, 35.2% and 12.4% of patients. Elevated symptoms of either anxiety, depression or both were found in respectively 28.6%, 3.0% and 15.9% and did not differ between patients <18y and >18y. Active disease was a significant risk factor for depressive symptoms (OR 4.6, p<0.001). Significant risk factors for anxiety and anxiety and/or depression were female gender (OR 1.7), active disease (OR 1.9) and a shorter disease duration (OR 1.4) (all p<0.025).

Conclusion: Considering the high prevalence of anxiety and depressive symptoms, screening is recommended in young IBD patients. Physicians should be aware that female patients and patients with active disease are the most vulnerable.

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**Objectives and Study:** Loss of response (LOR) to biological therapies is a big concern in inflammatory bowel disease (IBD) management and especially among paediatric patients where treatment options are limited. Therapeutic drug monitoring has been proposed as one of the ways to improve outcome, but its role remains unclear. The aim of this study was to determine whether infliximab (IFX) trough levels (TL) correlated with clinical and biological remission. We hypothesized that IFX TL after induction are predictive for IFX efficacy.

**Method:** All paediatric IBD patients with IFX TL available at their first maintenance infusion and a follow-up of at least 54 weeks were included. IFX induction regimens could be intensified at the discretion of the treating physician based on disease severity. All children received pro-active drug monitoring in the maintenance phase with the therapeutic window defined between 3-7 µg/mL (conform adult studies). Demographics, disease activity indices and inflammatory biomarkers were recorded retrospectively. Clinical remission was defined as PUCAI/PCDAI < 10 and biological remission as CRP ≤ 5 mg/L and ESR ≤ 10 mm/h at week 54. Patients were considered in deep remission if both criteria (clinical and biological remission) were met. IFX TL were measured by Ridascreen IFX Monitoring ELISA. Results were analysed using Mann-Whitney U-test. All data are presented as median [IQR] and alpha was set at 0.05.

**Results:** We included 25 children (15 with Crohn's disease and 10 with ulcerative colitis; 40% male). IFX was stopped in only 1 patient before week 54 due to LOR. Median age at start of IFX was 12.7 years [9.7-15.0] with a median disease duration prior to starting IFX of 7 months [4-12] and a median follow-up under IFX of 23 months [16-43]. At start of maintenance therapy, 76% was on concomitant immunosuppressants, which dropped to 36% at week 54. Median IFX TL at the time of the first maintenance infusion were significantly higher in children who were in clinical remission (3.4 µg/mL [2.4-6.0] vs 1.5 µg/mL [0.7-3.2], p=0.014), biological remission (3.8 µg/mL [2.7-9.0] vs 1.4 µg/mL [0.3-3.0], p=0.003) and deep remission (4.8 µg/mL [2.4-12.0] vs 2.3 µg/mL [0.9-3.2], p=0.008; see figure) at 54 week.

**Conclusion:** Paediatric IBD patients with enough exposure during induction therapy (deduced by the IFX TL at start of maintenance) have better chance for clinical and/or biological remission at week 54. This illustrates that sufficient exposure during induction is essential for a long and better response.
Disclosure of interest: I. Hoffman: Nutrica, nestlé, Mead Johnson, Abbvie; A. Gils: MSD, Janssen Biologicals, Pfizer, Takeda, Abbvie, R-biopharm, apDia, Merck; M. Ferrante: Takeda; Abbvie, Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, MSD, Pfizer; Chiesi, Tillotts, Zeria; S. Vermeire: Takeda, MSD, Abbvie, Pfizer; Ferring, Shire, Janssen, Pfizer Inc, Galapagos, Genentech/Roche, Celgene, Mundipharma, Eli Lilly, Second Genome, GSK; Dr. Falk Pharma, Hospira, Pfizer Inc and Tillotts

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**Objectives and Study**: The aim of the study was to report our long-term experience with the use of thalidomide on young children and adolescents patients with inflammatory bowel disease (IBD).

**Method**: A retrospective analysis of IBD patients treated by thalidomide from November 2006 and May 2017 at a tertiary care children's hospital was conducted. The clinical information and outcomes were recorded at each visit. Clinical remission was defined as Paediatric Crohn's Disease Activity Index (PCDAI) less than 10.

**Results**: Seventy-two IBD patients aged less than 20 years old were identified in this study with a median of 8.19 years old. The median follow up period from the initiation of thalidomide was 24.03 months (range, 3-77 months). Twenty of them were diagnosed with very early onset IBD caused by monogenic disease. About 58% of patients had disease localized to the ileum and colon, 38% were involved in colon only. Among all, 22 patients were treated with anti-tubercular drugs before, 6 cases failed to respond to infliximab. Clinical remission was achieved in 53 patients (73.61%) within one year. In patients who were concomitantly treated with steroids, 78.3% of them were able to stop steroids. An adverse event occurred in 30.56% of patients. Electromyography was performed on 16 patients, 5 of them were positive.

**Conclusion**: Although side effects may limit its long-term use, thalidomide is an effective therapy to induce clinical remission in selected refractory IBD patients.

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Does the circadian clock have a role in the pathogenesis of Inflammatory Bowel Disease (IBD)?

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Objectives and Study: Sleep dysfunction modifies the immune system and has been implicated as a potential trigger of IBD flares. Sleep dysfunction also alters the synchrony among clock genes leading to disruption of overall circadian regulation. Specifically, in the intestine, it is manifested by increased gut cellular permeability. We hypothesized that changes in mucosal immune balance may be reflected by alterations in the circadian clock and constitute an unattended pathogenic mechanism of IBD. Our aim was to investigate intestinal and systemic clock gene expression in patients with newly diagnosed IBD and in healthy controls.

Methods: Patients and controls were recruited upon diagnostic endoscopic evaluation. Demographics, familial medical history, sleep questionnaires, disease activity indices and endoscopic scores were recorded. Anthropometric parameters, C-reactive protein (CRP), albumin, haemoglobin (Hb) and fecal calprotectin (Fcal) were measured as well. Peripheral blood and tissue samples were analyzed for clock gene (Clock, Bmal1, Cry1, Cry2, Per1 and Per2) expression.

Results: Of the 32 participants recruited (age 8-25 years, median: 16.1), 14 had newly diagnosed IBD and 18 were healthy controls. Age, gender, sleep questionnaire scores and time of endoscopy were not statistically different between the groups. Hb, CRP and Fcal levels were significantly higher in the IBD compared to the healthy controls group (p<0.05), while albumin was significantly lower (p<0.05). Clock gene expression (Clock, Cry1, Cry2, Per1 and Per2) in WBC was decreased in newly diagnosed IBD patients compared with health controls (p<0.05). Similarly, the expression level of the aforementioned genes was lower in inflamed intestinal tissues (p<0.05). Interestingly, similar reduction in clock gene expression was seen even in healthy (non-inflamed) intestinal tissue from IBD patients (p<0.05).

Conclusions: Clock gene expression is reduced in both inflamed and non-inflamed intestinal tissue in patients with newly diagnosed IBD. Moreover, IBD patients show a systemic reduction in clock gene expression. Our findings may lead to new therapeutic approaches and strategies as well as serve as diagnostic tools in IBD.

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Disease and patient specific knowledge in teenage patients with inflammatory bowel disease - assessing readiness for transition

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Objective and Study: Inflammatory bowel diseases (IBD) present at age < 20 years in 25% of patients and successful transition to adult IBD clinics is imperative for treatment continuity. Data regarding knowledge and ability of disease self-management by teenagers is scarce. We aimed to assess the knowledge of teenage IBD patients about their disease, and their ability for independent disease management.

Methods: During a clinical visit, IBD patients aged 14 -18 years completed questionnaires, which included data on disease history, medications, and general knowledge about IBD. Patients over 16 years answered questions evaluating self-management skills. The answers were compared to the information in the medical records, and were graded with a Lickert scale with points given for each correct answer.

Results: 80 teenage patients aged 15.7 ± 1.2 years, were included, 54 (67.5%) with Crohn disease and 23 (28.7%) with ulcerative colitis. Age of diagnosis was 12.9 ± 2.61 years. Seventy-seven patients (96%) had a good knowledge of their disease history, 75 (94%) could correctly list their drug names, however only 53 (66%) knew their current drug dosages. Only a third of patients knew the effect of smoking (n=27, 34%) and alcohol (n=28, 35%) on their disease. None of the patients over 16 years were involved in scheduling their own appointments, and 72% read about their disease, mostly on the internet. The disease affected eating habits, social interactions, academic activities, and sports in a minority of teenage patients.

Conclusions: Medical providers should provide disease and patient specific information to teenage patients with IBD, as well as promote self-efficacy skills, in order to reinforce readiness towards transition.

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Audit of referral to Leicester Children’s Hospital for suspected Inflammatory Bowel Disease (standard 5 of new BSPGHAN / RCPCH quality standards)

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Objectives and Study: In January 2017 the new BSPGHAN / RCPCH quality standards were published for paediatric gastroenterology, hepatology and nutrition. The first step to implementation is to audit current practice. We present an audit of Standard 5 “Children with suspected inflammatory bowel disease are seen by a specialist service within four weeks in an age appropriate facility by a multi-disciplinary team”

The aim of the audit was to see how we performed during 2016-2017 compared to this standard of care, in order to see what changes we may need to make to improve.

Methods: We used our IBD database to identify children diagnosed with IBD over 2016 and 2017. We used the HISS system to note the date the original referral was received, the date they were seen either as an inpatient or in outpatients

Information about all suspected cases is not easy to obtain, so a decision was made to start with those cases we confirmed with IBD in 2016 and 2017 (up to November, December data to follow) to see how we performed with these cases in the first instance. We aimed to look at the cases where there was most delay to see how we can reduce this.

Cases diagnosed in the private sector, or those with incomplete information, were excluded.

Results: In Leicester Royal Infirmary, in 2016-2017:-

Total patients diagnosed with IBD = 62

Incomplete information 1, diagnosed privately 4, leaving 57 patients

<table>
<thead>
<tr>
<th>Time seen</th>
<th>Number (percentage) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>As an inpatient</td>
<td>12 (21%)</td>
</tr>
<tr>
<td>After 28 days or less</td>
<td>29 (51%)</td>
</tr>
<tr>
<td>After 28-42 days</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Over 42 days</td>
<td>54d, 55d, 62d, 68d, 96d (9%)</td>
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Summary: Out of 57 patients diagnosed with IBD in 2016-2017 in NHS 72% met the new quality standard, with 91% seen within 6 weeks.

5 patients waited longer. None were felt very unwell when first seen.

Conclusions:
1) In our centre we meet the suggested standard in 72% of cases, and are close to this in a further 19%
2) This was achieved by consultants doing many extra adhoc clinics. The appointment of a 4th consultant should help us to get even closer to the standard
4) The children who waited were felt not to be so unwell according to the information on the referral letter, or family cancelled appointment initially, so we will consider education to GPs and general paediatricians regarding information we would find helpful in referral letters
5) The next step would be to audit all suspected cases, but this information is not easy to obtain retrospectively


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Study on association of HLA class I alleles with pediatric Crohn’s disease in China

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Objectives and Study: To analyze association between HLA class I (HLA-I) predisposing alleles and clinical characteristics of pediatric Crohn’s disease (CD) in Chinese Han population.

Method: We investigated genotypes for HLA-I alleles in 100 unrelated Han children patients with CD by PCR-SSO. The distributions of HLA-I alleles phenotypic frequencies were further analyzed according to gender, onset age and disease location. These data were compared with healthy controls of 279 Chinese Han people, their HLA-I alleles genotypes were based on NCBI MHC database.

Results: 1. Association of HLA-I alleles with CD: Compared with controls, phenotypic frequencies of HLA-A*02:01 (27.0% vs. 10.0%, OR=3.32, Pc=4.7E-04), HLA-A*11:02 (9.0% vs. 1.4%, OR=6.80, Pc=0.013), HLA-B*15:11 (8.0% vs. 0.4%, OR=24.17, Pc=2.4E-03), HLA-B*37:01 (5.0% vs. 0.0%, OR=32.19, Pc=0.018) and HLA-C*06:02 (18.0% vs. 5.4%, OR=3.86, Pc=1.2E-03) were significantly increased in CD, whereas HLA-A*02:03 (5.0% vs. 19.7%, OR=0.21, Pc=7.1E-03) was highly decreased.

2. Association between HLA-I predisposing alleles and clinical characteristics of CD: Compared with controls, there were no significant difference between HLA-I predisposing alleles and patients’ onset age and gender. The phenotypic frequency of HLA-B*37:01 (10.0% vs. 0.0%, OR 71.15, Pc=0.018) was significantly increased in CD with ileocolonic disease, and HLA-A*02:01 (16.4% vs. 10.0%, OR=4.48, Pc=0.013), HLA-B*15:11 (7.5% vs. 0.4%, OR=49.64, Pc=9.90E-04) and HLA-C*06:02 (11.9% vs. 5.4%, OR=5.63, Pc=0.010) were increased in CD with upper gastrointestinal disease.

Conclusion: We identified five susceptibility HLA-I alleles, HLA-A*02:01, HLA-A*11:02, HLA-B*15:11, HLA-B*37:01 and HLA-C*06:02, and one protective alleles, HLA-A*02:03 for pediatric CD. HLA-A*02:01, HLA-B*15:11, HLA-B*37:01 and HLA-C*06:02 were also associated with diseased location of CD.

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-385

Founder mutation in IL10RA in Chinese patients with very early onset inflammatory bowel disease

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Objectives and Study: In China, very early onset inflammatory is mostly seen in patients with IL10RA mutations. Among all pathogenic mutations described so far, the p.R101W mutation stands out as the most frequent one and is particularly associated with patients of Chinese origin. We aimed to investigate existence of a potential founder effect of p.R101W mutation in the Chinese population.

Method: We genotyped 11 patients with pathogenic IL10RA p.R101W mutations and compared disease haplotypes with ethnically matched controls. Haplotype analysis was performed.

Results: Haplotype analysis revealed a shared segment only in these patients, which was not found among controls.

Conclusion: IL10RA p.R101W occurs as a founder mutation in Chinese population.

[Haplotypes of the alleles with p.R101W mutation in IL10RA gene.]

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GASTROENTEROLOGY - Inflammatory bowel disease

G-P-386

High body mass index and anemia at diagnosis are predictors of extra-intestinal manifestations in children with inflammatory bowel disease

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Objectives and Study: Extra-intestinal manifestations (EIM) are common in inflammatory bowel disease (IBD). Although well-investigated, the current ability to predict occurrence of EIM, especially among children, is poor. The aim of our study was to define predictors for EIM in children with IBD.

Methods: We included children with IBD from the pediatric gastroenterology unit, "Dana-Dwek" children's hospital, in the years 2010-2016. We retrospectively compared demographic and disease variables at diagnosis between children with and without EIM. Children were categorized in quartiles according to body mass index (BMI) percentiles at diagnosis. Disease activity was evaluated by the pediatric Crohn's disease/Ulcerative Colitis activity indices (PCDAI/PUCAI).

Results: One hundred children were evaluated: 62 with Crohn's disease and 38 with Ulcerative Colitis. The median age (IQR) at diagnosis was 13.9 (11.9-15.2) years. Ten children (10%) presented with EIM at diagnosis and additional 36 children (36%) exhibited EIM during median (IQR) follow-up of 2.1 (1.2-3.8) years. The most common EIM were aphthous stomatitis (18%), arthralgia (14%), skin manifestations (8%) and arthritis (6%). Variables at diagnosis that were associated with occurrence of EIM during follow-up were BMI in the lower or upper quartile (HR 9.3 and 23.7, respectively, P<0.001), moderate to severe disease activity (HR 4.4, P<0.001), anemia (HR 2.3, P<0.001), abnormal C-reactive protein (HR 1.04, P<0.001) and extensive involvement in Crohn's disease (HR 3.4, P=0.025). In a multivariate analysis, anemia (HR 2.1, P<0.001) and BMI in the upper quartile (HR 3.54, P=0.004) at diagnosis were associated with EIM.

[Time to EIM by BMI at diagnosis]
**Conclusion:** Several predictors for EIM in children with IBD were identified. Further studies are needed to elucidate whether children with high risk for EIM should be treated more aggressively from diagnosis.

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**Objectives and Study:** Stepping down from combination therapy of anti-TNF and immunomodulator drug to monotherapy is common practice in IBD. The aim of our study was to define risk factors for disease exacerbation after withdrawal from combination therapy in children with IBD.

**Methods:** We retrospectively compared disease course between children with IBD who stepped down to anti-TNF monotherapy (group 1) and children who continued combination therapy until the end of the study follow-up (group 2). In order to define risk factors for disease exacerbation after stepping down, we compared clinical data between children who exacerbated and children that kept disease remission.

**Results:** Sixty-four patients were included: 32 in group 1 and 32 in group 2, with median (IQR) age of 16 (13.4-17.5) years and mean (range) follow-up of 19.1 (6.5-24) months. The median (IQR) duration of combination therapy was 6 (6-10) months for children who stepped down. In a multivariate analysis, the risk for disease exacerbation and hospital admissions was significantly higher in group 1 compared to group 2 (OR 4.35, p=0.01 and OR 3.13, p=0.045, respectively). Penetrating phenotype, upper GI involvement, moderate-severe disease activity at diagnosis, treatment with Infliximab, sub-therapeutic anti-TNF levels and high stool calprotectin during combination therapy were associated with disease exacerbation and hospital admissions after stepping down to monotherapy.

**Conclusion:** Children with IBD are at higher risk of disease relapse after stepping down from combination to monotherapy. Several risk factors for disease relapse after cessation of combination therapy were identified.
Body mass index in the lower or upper quartile is a marker of severe disease course in children with Inflammatory Bowel Disease

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Background: Inflammatory Bowel Disease (IBD) has been historically associated with underweight and malnutrition, but obesity is emerging as a significant problem in IBD. It is uncertain how body mass index (BMI) affects the clinical course of the disease. The aim of our study was to describe the association between BMI at diagnosis to disease course.

Methods: We reviewed the medical records of children with IBD from the pediatric gastroenterology unit, “Dana-Dwek” children’s hospital, in the years 2008-2016. Demographic and anthropometric data was collected as well as disease characteristics, course and treatment. Patients were categorized in quartiles according to BMI percentiles at diagnosis (Q1-Q4). Disease activity at diagnosis was evaluated by PCDAI or PUCAI.

Results: One hundred patients were evaluated: 62 with Crohn’s disease and 38 with Ulcerative Colitis. The median age (IQR) at diagnosis was 13.9 (11.9-15.2) years. The median follow-up (IQR) was 2.1 (1.2-3.8) years. At diagnosis, 46% were in Q1, 20% in Q2, 19% in Q3 and 15% in Q4. Long duration of symptoms before diagnosis and high disease activity at diagnosis were associated with BMI in Q1 and Q4 (p< 0.001). In a multivariate analysis, BMI in the lower and upper quartiles was associated with shorter time to exacerbation (HR 3.2 and 4.7, respectively, p=0.016) and use of biologic drugs (HR 4.5 and 4, respectively, p=0.021).

Conclusions: BMI in the lower and upper quartiles was associated with more severe disease course in children with IBD. BMI may serve as an easy and available predictor of IBD prognosis.

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Characteristics of fecal microbiota in pediatric Crohn's disease and their dynamic changes during infliximab therapy

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Objectives and Study: Crohn's disease (CD) is known to be associated with gut microbial dysbiosis that is represented by decreased biodiversity and imbalances in the intestinal microbiome. Infliximab (IFX) is increasingly used to treat pediatric CD, however it is not clear how gut microbiota is modified during IFX treatment. The aim of this study is to characterize the fecal microbiota community composition in pediatric CD patients and to assess its dynamic changes during IFX therapy.

Method: Fecal samples were collected from 11 pediatric CD patients prior to and during IFX therapy, and from 16 healthy children. 16S rRNA sequencing approach was applied to determine the compositions of microbial communities in fecal samples. The composition and function of the fecal microbiota were compared between CD patients and health controls.

Results: Characteristics of fecal microbiome composition in pediatric CD patients prior to IFX treatment were represented by a lower biodiversity, a gain in Enterococcus, and a significant loss in multiple short-chain fatty acid (SCFA)-producing bacteria, including Anaerostipes, Blautia, Coprococcus, Faecalibacterium, Lachnospira, Odoribacter, Roseburia, Ruminococcus, and Sutterella. Additionally, alterations were observed in metabolic functions of the gut microbial community in CD. IFX treatment increased the biodiversity of gut microbiota and shifted its composition as well as its functional capabilities in the pediatric CD patients toward a healthy status. However, multiple SCFA-producing taxa were not significantly expanded. The sustained response of pediatric CD patients to IFX was associated with abundance of SCFA-producing bacteria.

Conclusion: A lower biodiversity with alterations in the composition and function of fecal microbial community, characterizing gut microbial dysbiosis, were observed in the Chinese pediatric CD patients. IFX diminished the CD-associated gut microbial dysbiosis but was deficient in increasing certain SCFA-producing taxa. Expanding SCFA-producing bacteria prior to and during IFX therapy may help to sustain therapeutic response.

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Current status of the first and second line therapy for Helicobacter pylori infection in symptomatic children: a single center study

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Introduction: Current evidence suggests the decline of the eradication rates of H pylori in children treated with standard first line therapy, partly determined by its antibiotic resistance.

Aims & Methods: To evaluate the effectiveness of current first and second-line therapy recommendations for H pylori eradication in children. We conducted a prospective open-label study of 158 symptomatic children (age range 6 months - 18 years; 106 girls) who required a first upper digestive endoscopy over the past year. Active H pylori infection was documented in 122 of the 158 investigated children (77.2%). Infected children were randomly assigned to receive either a 7-14 days standard empiric triple therapy consisting of esomeprazole (ESO) plus amoxicillin (AMO) and clarithromycin (CLA) or metronidazole (MET), either a sequential therapy for 10-14 days. Bismuth salts are not easily available in our country. Eradication efficacy was assessed by follow-up endoscopy 4-8 weeks after the end of anti-H pylori therapy by at least two different invasive tests. In patients failing to be cured through the first treatment a second alternative was applied (a triple therapy based on quinolones or metronidazole either sequential therapy) associated with antibiotic susceptibility testing. The primary and secondary outcomes were the rate of H pylori eradication after the first and second line therapy, by intention to treat (ITT) and per-protocol (PP) analysis. Statistical analysis was performed with EPI INFO 7. The differences between eradication rates were analysed by χ² test and the Odds Ratio.

Results: Patients with H pylori infection were treated with an initial empiric first line standard therapy (n=52) or a sequential therapy (n=70). Of the 122 children, 9 patients were lost to follow-up (7.38%). Overall H pylori was eradicated in 87/122 children (71.32% for ITT analysis versus 76.99% for PP analysis). The first eradication rates were significantly higher using the sequential therapy (55/70 cases; 78.57% for ITT analysis and 55/64 cases; 85.93% for PP analysis) compared with standard first line triple therapy (32/52 cases; 61.53% for ITT analysis and 32/49 cases; 65.30% for PP analysis). The ITT and the PP eradication rates were significantly higher with sequential treatment (OR= 0.43; 95% CI: 0.19-0.97; p= 0.04; χ²= 3.43; p= 0.06 for ITT analysis and OR= 0.30; 95% CI: 0.12-0.77; p= 0.013; χ²= 5.55; p= 0.01 for PP analysis). A second-line therapy was recommended in 26 of cases with an overall eradication rate of 80.76% for ITT analysis and respectively 87.5% for PP analysis. The choice of second line therapy was tailored by antimicrobial susceptibility only in some cases (57.7%). The eradication rates for PP analysis were: 90% for triple therapy based on MET and 80% for quinolones and respectively 80% for sequential therapy.

Conclusion: This endoscopic series reveals a high rate of H pylori infection (77.2%). The sequential therapy achieved a significantly higher rate of eradication than the standard empiric triple regimens regardless of using ITT (78.57% versus 61.53%) or PP (85.93% versus 65.30%) analysis. The eradication rates for the second-line therapy was significantly higher (87.5% for PP analysis) compared with the first-line empiric standard therapy (76.99% for PP analysis).

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Histological changes of Helicobacter pylori associated gastroduodenal disease and dyspepsia in Armenian children

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Objectives and Study: Helicobacter pylori (Hp) infection is usually acquired early in childhood and leads to development of chronic gastritis and - in paediatric patients - rare complications such as peptic ulcer disease and atrophic gastritis. Considering the high rate of gastric malignancies in the adult population in Armenia, we aimed to determine the rate of Hp associated atrophic gastritis, metaplasia and dysplasia in Armenian children with gastroduodenal disease and dyspepsia.

Methods: One hundred twenty patients (54 males and 66 females, mean age 10.4±3.1 years) with complaints of recurrent epigastric pain and dyspepsia, referred to a tertiary paediatric medical center, were involved in the study. All patients underwent esophagogastroduodenoscopy with biopsies: 2 from the antrum (1 for rapid urease test and histology, 1 for Hp culture), 1 from the duodenal bulb and the distal esophagus. Hp associated gastroduodenal disease (GDD; presence of erosions or ulcer in the stomach and/or duodenum, proven Hp infection by 2 invasive tests) and functional dyspepsia (FD; no lesions in the stomach and duodenum, proven or excluded Hp infection by 2 invasive tests) were diagnosed in 61 (50.8 %) and 59 (49.2%) patients respectively. Histology was assessed according to the updated Sydney system: atrophy was defined as the loss of normal glandular components with or without replacement with fibrosis and/or intestinal metaplasia. Degree of atrophy was evaluated using the 0-3 scoring scale. Gastric and duodenal biopsy specimens were stained by Giemsa modification for Hp infection. One antral biopsy was cultured in Hp selective media.

Results: Twenty-two (26.4%) of 120 patients had gastric or duodenal histological changes: 12 with Hp associated GDD and 10 with FD. Main symptoms were nausea and/or recurrent epigastric pain (mean duration 20 months). These patients were divided into 2 subgroups: 1st - gastric changes and 2nd - duodenal changes. Hp associated GDD and FD patients ratio in the 1st group was 5:5 and in the 2nd group 7:5. All patients in 1st subgroup but only 1 in the 2nd subgroup were Hp positive. In the 1st subgroup distribution of histological changes was: 5 (6%) atrophic gastritis, 3 (3.6%) mild dysplasia of glandular epithelium and 2 (2.4%) intestinal metaplasia. Furthermore, the predominance of non-erosive gastritis (7 patients) compared to erosive gastritis (3 patients) was observed. The degree of gastric atrophy was assessed as mild (score1) in 4 patients and as moderate (score 2) in 1 patient. The 2nd subgroup of patients with duodenal complications included 12 (15.6%) children with gastric metaplasia of duodenum. In this subgroup we noticed the prevalence of erosive duodenitis (8 patients) over non-erosive duodenitis (4 patients). The degree of gastric metaplasia was assessed as mild in all of them.

Conclusions:

- A high frequency of significant histological changes of the stomach were observed in our cohort of patients with Hp associated GDD and FD.
- These histological data did not always correlated with the severity of endoscopic lesions. In the subgroup of patients with gastric histological changes the predominance of non-erosive gastritis compared to erosive gastritis was noticed.
- Almost equal histological rate of changes in patients with Hp associated GDD and FD were noted.

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The nutritional effects of Helicobacter pylori infection in symptomatic children admitted in a digestive unit

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Introduction: Helicobacter pylori (H pylori) infection affects about 30% to two-thirds of human populations and has a significant impact on gastrointestinal system associated with extraintestinal manifestations, which depend on the time of acquisition and of the eradication. There are conflicting results regarding the nutritional effects of H pylori infection in children, mostly about the reduced bioavailability of essential nutrients with growth impairment. The role of H pylori in the association with iron deficiency anaemia is of considerable current interest.

Objectives: To evaluate the effects of H pylori infection on the nutritional and the iron status of symptomatic children that required a first upper endoscopic evaluation.

Methods: This was an observational prospective study of 406 symptomatic children (254 girls, age, range 6 months-18 years, sex ratio female/male = 1.67) mostly with uninvestigated dyspepsia or extradigestive signs suggestive for organic disease, admitted in our digestive endoscopy unit, from January to December 2016. Socioeconomic status, medical and clinical data were analysed. Weight, height, body mass index (BMI) for age and sex were used according to growth charts provided by WHO, 2007, because Romania is in a nutritional transition and does not have updated national growth charts. H pylori infection was documented by at least two standard invasive tests. Hematologic parameters and nutritional status were compared in patients with and without H pylori infection. Chi-squared test was used for statistical analysis. A p-value less than 0.05 was considered as statistically significant.

Results: Active H pylori infection was documented in mostly of studied patients (251 of 406 children: 61.8%). The socioeconomic status was low in the majority of cases (239 of 406 children: 58.86%). The majority of patients presented normal nutritional status (252 of 406 cases: 62.02%), with a significant proportion of wasting (13.05%) associated with risk to underweight (12.8%) overweight (9.85%) and obesity (2.22%). The prevalence of undernutrition was higher in children not infected with H pylori compared to those infected (12.7% versus 13.54%; p=0.93). Unexpectedly the prevalence of overnutrition was higher in the case of the H pylori positive children compared to the negative ones (9.16% versus 4.52%, p=0.24). The stunted was observed only in 3.8%cases. Iron deficiency anaemia was found in 64 of 406 cases (15.76%), most frequently in infected H pylori patients (44 of 251 cases; 17.52%) compared to uninfected children (20 of 155 cases; 12.90%), p= 0.27.

Conclusions: The H pylori prevalence rate (61.8%) revealed by our study suggests that this infection remains a semnificative problem in our country. This endoscopic series revealed a coexistence of undernutrition with overnutrition in symptomatic H pylori infected children, but without statistically signification for the both ends of the spectrum of poor nutritional status (p= 0.93, respectively p= 0.24) compared with uninfected ones.

Contrary to other observational studies, our study showed that the presence of iron deficiency anaemia was not significantly higher in infected H pylori children compared to uninfected patients (17.25% versus 12.90%, p= 0.27).

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Objectives and Study: This first study aims to evaluate sleep quality and quality of life in adolescents with chronic gastritis and to determine the related factors.

Method: Clinically and histopathologically chronic gastritis-diagnosed patients with upper gastrointestinal system endoscopy who were admitted with gastrointestinal symptoms were included in the study. The Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale were used to assess sleep quality, and the quality of life scale for the appropriate age group was used to determine the quality of life. Control group included healthy volunteers with no chronic disease and no complaints of gastrointestinal system. Sleep and quality of life and related factors were assessed in these patients.

Results: 56 patients with gastritis and 55 healthy volunteers were included in the study, with similar age and gender distributions. In patients with gastritis, 60.7% had dyspepsia, 30.4% had abdominal pain, 30.4% had vomiting, 17.9% had nausea and 10.7% had swelling in the abdomen. Patients with gastritis were found to have significantly lower overall quality of life, subscale and total scale scores except for social functioning total scores. Except for the subjective sleep quality, a significant difference was found in the sleep quality in subscale, total scale and sleepiness scale point average of patients with gastritis between the groups when compared with the healthy control group. There was no significant difference in terms of quality of life, sleep quality and sleepiness subscale scale and total scale scores (p = 0.28, p = 0.17, p = 0.63) in 19.6% of patients with obesity or overweight gastritis compared to patients with other gastritis. There was no significant difference was found between Helicobacter Pylori positive (44.6%) and negative gastritis patients in terms of total quality of life and sleepiness scale scores (p = 0.89, p = 0.38). There was a significant difference in sleep quality between the two groups in terms of subscale score of sleep duration (p = 0.029), however no significant differences in terms of other sub-domains and total scale scores (p = 0.96).

Conclusion: It is the first study evaluating quality of life and sleep quality in adolescent age group with gastritis. Low life and sleep qualities detected in adolescents with gastritis show the importance of correct diagnosis and appropriate treatment in these patients.

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Is there any relation between extrinsic host factors and Helicobacter pylori antibiotic resistance patterns in children?

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Objectives and Study: The decreasing Helicobacter pylori eradication rates, with classical treatment observed in the last decade, are highly dependent on antibiotic resistance. Although the overall H. pylori prevalence seems to decrease, common occurrence of treatment failure is a growing problem necessitating detailed evaluation of factors involved in antibiotic resistance. Association of resistance with bacterial traits such as virulence factors and intrinsic host factors such as genetic polymorphisms have been investigated in several studies but most host factors have not been evaluated adequately. In this study we aimed to evaluate the current antibiotic resistance patterns of H. pylori strains isolated from our infected paediatric patients and impact of possible demographic and extrinsic host factors, if there is any.

Method: This is a retrospective study of H.pylori infected children in whom the bacteria has been grown in gastric mucosal biopsy samples during a two years period. All biopsy specimens obtained from children with clinical or endoscopic findings suggestive of H. Pylori gastritis were cultured on Columbia agar with 5% defibrinated horse blood and incubated at 37 °C in a micro aerobic atmosphere up to 7 days. H. pylori was identified using conventional methods. MIC values of the strains to amoxicillin (AMX), levofloxacin (LEV), clarithromycin (CLA), tetracycline (TET) and metronidazole (MET) was investigated with gradient test [E -test (Biomerieux,France)] and evaluated according to the European Committee of Antibiotic Susceptibility Testing (EUCAST) criteria. Antibiotic susceptibility was studied for clarithromycin (CLA), metronidazole (MET), levofloxacin (LEV), amoxicillin (AMX) and tetracycline (TET). Demographic characteristics, comorbidities, number of previous endoscopies, infection rates per year, antibiotic use, number of family members and siblings living in the same house were recorded.

Results: Overall H.pylori was grown in culture in 33 of 110 gastric biopsy samples. Of these thirty-three, 26 samples were available for the analysis of antibiotic resistance. Only 8 samples (30.8 %) had H.pylori susceptible to all antibiotics. Resistance to only any one antibiotic was observed in 12 ( 46.1 %), resistance to any two antibiotics in 5 (19.2 %) and resistance to any four antibiotics in 2 (7.7 %). CLA resistance and MET resistance were unacceptably high (57.7 % and 40 % respectively) whereas AMX and TET displayed a more favourable resistance pattern (both 3.4 %). Two multi resistant H.pylori strains were isolated from an anorexia nervosa patient (no antibiotic use in the preceding year) and a subacute sclerosing panencephalitis patient (high rate of antibiotic use: 6 courses/year). No statistical association was noticed between the frequency of antibiotic usage, number of family members, number of previous endoscopies and antibiotic resistance.

Conclusion: In our geographic area, CLA resistance and MET resistance are at the critical threshold of 40 % rendering these drugs inappropriate for primary H. pylori eradication therapy. No clear extrinsic host factors could be shown to be involved in this high resistance rates. There is urgent need to change the primary eradication therapy protocols for children according to our resistance results.
Correlative research of Interleukin-1B alleles with helicobacter pylori infection and immune thrombocytopenia purpura in children

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Objectives and Study: Polymorphism at positions IL-1B(-511 and -31) will be analysed to explore the relevant genes for both susceptibility and protective genes in HP (Helicobacter pylori) patients, ITP (Immune thrombocytopenia) patients, HP+ITP patients and healthy children.

Method: From December 2015 to October 2016 we studied 126 patients (68 male, 58 female, range 2-16 years) who attended Beijing Children's Hospital, including HP patients, ITP patients, HP+ITP patients and healthy children. Venous blood from each child was collected into one EDTA containing sample collection tubes, each one 2 ml in volume. We record everyone's information and extract DNA from samples and analyze the polymorphisms at positions IL-1B(-511 and -31) by using PCR-SBT. Date analysis was performed on SPSS version 19.0.

Results:
1. Genotype frequencies of these two polymorphisms did not deviate significantly from Helsinki's Declaration in the group.
2. The genotypes of IL-1B-31 were CC, CT, TT, the distribution frequencies of IL-1B-31 were as follows: CC(15.9%), CT (62.7%), TT(21.4%). The genotypes of IL-1B-511 were CC, CT, TT, the distribution frequencies of IL-1B-511 were as follows: CC(21.4%), CT (62.7%), TT(15.9%).
3. In the study of 126 Han nationality children, there were 68 boys and 58 girls. The frequencies of IL-1B-31 between boys and girls were CC 14.7% and 17.2%, CT 60.3% and 65.6%, TT 25% and 17.2%. The frequencies of IL-1B-511 between boys and girls were CC 25% and 17.2%, CT 60.3% and 65.6%, TT 14.7% and 17.2%. There was no significant difference in the distribution of SNPS within IL-1B-31 and IL-1B-511 between boys and girls.
4. The pairwise comparisons in patients with H pylori-infected patients and healthy children showed that the distribution frequencies of IL-1B-31 were as follows: CC 9.4% and 21.9%, CT 53.1% and 65.6%, TT 37.5% and 12.5%, the frequencies of IL-1B-31 TT genotype were higher in HP patients than healthy group. The distribution frequencies of IL-1B-511 were as follows: CC 37.5% and 12.5%, CT 53.1% and 65.6%, TT 9.4% and 21.9%, the frequencies of IL-1B-511 CC genotype were higher in HP patients than healthy group.
5. The pairwise comparisons in patients with HP+ITP patients and ITP patients showed that the distribution frequencies of IL-1B-31 were as follows: CC 9.7% and 23.3%, CT 61.3% and 71%, TT 29.0% and 6.4%, the frequencies of IL-1B-31 TT genotype were higher in HP +ITP patients than ITP patients. The distribution frequencies of IL-1B-511 were as follows: CC 29.0% and 6.4%, CT 61.3% and 71%, TT 9.7% and 23.3%, the frequencies of IL-1B-511 CC genotype were higher in HP +ITP patients than ITP patients.
6. There was no significant difference in the distribution of SNPS within IL-1B-31 and IL-1B-511 between HP+ITP patients and HP patients, ITP patients and healthy group.

Conclusion:
1. The genotypes of IL-1B-31 and IL-1B-511 were both CC, CT, TT, CT genotype was the main genotype in this study.
2. In this study, the polymorphisms of IL-1B-31 TT, IL-1B-31 T, IL-1B-511 CC, IL-1B-511C alleles may be associated with the susceptibility of HP infection.
3. In this study, the polymorphisms of IL-1B-31 TT, IL-1B-31 T, IL-1B-511 CC, IL-1B-511 C alleles may be associated with HP infection in patients with ITP.
4. The SNPS of IL-1B-31 was related to the SNPS of IL-1B-511, they had the similar polymorphisms.

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**Objectives and Study:** The urea breath test is stated to be a sensitive and specific modality in the diagnosis of Helicobacter pylori (HP), although a “test and treat” strategy is advised against in the paediatric population. The benefits of HP eradication therapy is most evident in the presence of peptic ulcer disease. We aim to evaluate the diagnostic accuracy of the urea breath test, by correlating endoscopic and histological outcomes in children with a positive urea breath test.

**Method:** All children and adolescents, with a positive urea breath test, whom were undergoing concomitant (done just prior to, or shortly after) upper gastrointestinal endoscopy were recruited for this study. Urea breath testing is done via oral administration of a 75mg $^{13}$C urea substrate, and sequential exhalation measurements were performed at 10 minute intervals over 30 minutes. A positive test is defined as a delta over baseline (DOB) as 4.0 ‰ or higher; or 2.5 ‰ or higher if the child was exposed to proton-pump inhibitors, antacids or antibiotics in the last 4 weeks. During endoscopy, 3-4 biopsies from the antrum and corpus region are obtained for histopathology, with 2 additional biopsies for the rapid urease test; mucosal biopsies are also routinely obtained from the lower esophagus and duodenum. All statistical analyses were performed by STATA/SE 13.1.

**Results:** 109 children were recruited, of which the median(range) age was 13.0 (4.0-18.0) years, and males accounted for 37.6% of the cohort. 84.4% of children had dyspepsia or epigastric pain, 7.3% had vomiting and 3.7% had frank gastrointestinal haemorrhage. The median (interquartile range) DOB value was 9.4(4.6-66.9) ‰. Normal macroscopic endoscopic findings were seen in 29.4%; antral nodularity in 36.7%; peptic ulcer disease in 16.5%. The mean(range) DOB values amongst subjects with normal macroscopic endoscopy findings was 7.5 (2.8-41.5)‰. The rapid urease test was positive in 40.6%.

On histopathological examination, HP positive active chronic gastritis was seen in 43.1% of children; HP-negative chronic gastritis in 47.7%; gastroesophageal reflux disease and/or eosinophilic esophagitis in 12.9% and a normal histology(esophagus, stomach, duodenum) in 8.3%. Children with confirmed HP infection (either positive histopathology or positive rapid urease test) had significantly higher mean(range) DOB [26.8(2.6-78.0) v.s. 8.8(2.8-74.4) , p &LT; 0.001]. Children with antral nodularity likewise had significantly higher mean(range) DOB [28.9(3.5-78.0) v.s. 9.9(2.6-74.4), p&LT; 0.001] ; however, subjects with peptic ulcer disease(PUD) had no significant difference in DOB values (15.4 in PUD v.s. 17.2 in non-PUD, p=0.69).

**Conclusion:** Less than half (44.9%)of all children in our cohort, with a positive urea breath test had confirmed HP infection in our cohort ; a even smaller proportion of children (16.5%) had endoscopically proven peptic ulcer disease. These findings support evidence against the “test and treat” strategy for Helicobacter pylori, and emphasise the importance of an appropriately thorough diagnostic evaluation of dyspepsia to guide therapy.

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Helicobacter pylori infection and specific Immunoglobulin E antibodies to food allergens in symptomatic children admitted in a digestive endoscopy unit

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Introduction: Helicobacter pylori is one of the most widespread bacterial infections worldwide, therefore nowadays its prevalence was decreasing, mostly in developed countries. There are some studies which support that H pylori could favor the development of food allergy. As part of the hygiene hypothesis, many studies support the protective role of H pylori infection in the development of immunoglobulin E (Ig E) antibodies to food antigens.

Objectives: To assess the relationship between H pylori infection and specific immunoglobulin E (Ig E) antibodies to food allergens in symptomatic children.

Methods: We conducted a prospective study of 394 symptomatic children (249 girls, age range 6 months-18 years), mostly with uninvestigated dyspepsia requiring an endoscopic evaluation in our unit, from January to November 2016. All patients were evaluated for H pylori infection by at least two standard invasive tests and for specific immunoglobulin E antibodies to major food allergens (R-biopharm, Germany). The nutritional status of patients was assessed in all cases by the new World Health Organization (WHO, 2007) growth charts. EPI-INFO version 7 was used for statistical analysis. A two sided p-value less than 0.05 was considered statistically significant.

Results: Active H pylori infection was documented in 246 (62,3%) cases. The allergic sensitization to at least one of the food allergens was identified in 134 of 394 patients (34%). The majority of Ig E positive children (109 of 134 cases; 81.3%) were positive for cow's milk followed by egg (17.9%), wheat (7,46%), peanut (4,5%), soybean (3,73%). The allergic sensitization to food allergens was associated with abnormal levels of specific Ig E antibodies to common inhalatory allergens in 55 of 134 cases (41,04%). Regarding the association of H pylori infection with an elevated serum Ig E level to at least one of the food allergens tested, there was no significant correlation (p=0,14). Thus 77 of 134 (31,30%) patients positive for food specific Ig E antibodies were H pylori infected and 57 of them (38,55%) were H pylori negative (Fisher exact test= 0,08). The assessment of the patient's nutritional profile in relationship with H pylori infection and food allergy not revealed a statistically significant effect on the two ends of the poor nutritional status (undernutrition and overnutrition).

Conclusions: The H pylori prevalence rate highlighted by this endoscopic series (62,3%) revealed that the recent decline of H pylori infection observed in developed countries is not evident in our country. There was no significant correlation between H pylori infection and Ig E mediated food allergy in our patients (p= 0,45). The poor nutritional status (undernutrition and overnutrition) was not statistically significant associated with the H pylori infection and food allergy in our patients. It seems like other factors like genetic and environmental (diet, microflora, etc) can contribute to the increase of the prevalence of the allergic sensitization to the food allergens.

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GASTROENTEROLOGY - Peptic disease and helicobacter pylori

G-P-398

Clarithromycin resistance emerging within the frame of an unsuccessful eradication treatment in H. pylori infected children

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Objectives and Study: Clarithromycin-resistant Helicobacter (H.) pylori strains are more prevalent in patients previously treated for H. pylori infection compared to treatment-naïve patients. However, only limited data are available from longitudinal assessments of emerging clarithromycin resistance in pediatric patients based on pre- and post-treatment susceptibility testing. We aimed to determine the emergence of clarithromycin resistance in H. pylori infection within the frame of standard clarithromycin-containing triple therapy.

Method: Between 2004 and 2015, a total of 376 treatment-naïve children with H. pylori infection as shown by gastric tissue culture, followed by susceptibility testing, or real-time stool PCR, which allows also for detection of clarithromycin resistance, were retrospectively identified. Of these, 90 children (23.9 %) with primary clarithromycin resistance and 59 children without a clarithromycin-containing therapy were excluded from further analyses. The remaining 227 children were prescribed a standard 7-day clarithromycin-containing triple therapy. In 205 children results of urea breath tests and/or monoclonal stool antigen tests, which had been performed to confirm H. pylori eradication, were available. In all cases of treatment failure (n=44) clarithromycin susceptibility re-testing with gastric tissue culture (n=9) and/or stool PCR (n=43) had been performed within a median of 9.5 weeks (range, 4-25 weeks).

Results: H. pylori eradication was achieved in 161/205 (78.5 %) children. In 17 (38.6 %) of 44 children with persistent H. pylori infection clarithromycin resistance had emerged within the frame of the first-course treatment.

Conclusion: Emergence of clarithromycin resistance was observed in more than one third of H. pylori infections with sensitive strains after treatment failure within the frame of the first-course treatment.

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GASTROENTEROLOGY - Peptic disease and helicobacter pylori

G-P-399

Helicobacter pylori reinfection rates in children after eradication therapy in Iran

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Objectives and Study: Children differ from adults with respect to H pylori infection in terms of the prevalence of the infection, the complication rate, the near-absence of gastric malignancies, age-specific problems with diagnostic tests and drugs, and a greater rate of antibiotic resistance. Considering the few studies done to evaluate the recurrence of this microorganism in Iran and considering that Helicobacter pylori recurrence in developed countries is higher. This study was done To investigate the recurrence rate of this microorganism and possible variables that may effect on it.

Method: This is a descriptive, analytical, prospective study. Since April, 2015, for 18 months according to inclusion and exclusion criteria, 74 children with Helicobacter pylori positive in endoscopy and pathology have been studied in Children hospital, Tabriz, Iran. These children were treated with Helicobacter Pylori eradication protocol and then re-examined at intervals of six months and one year later to evaluate relapse of infection by Helicobacter pylori antigen test in stool. Other variables such as age and sex and patients’ living conditions have also been studied.

Results: Of the 74 patients with helicobacter pylori infection, six months later, 59 cases were negative for Helicobacter pylori, but 15 cases after six months were positive for Helicobacter pylori, which is 19.4% patient/year. We excluded these 15 patients and then one year after eradication we reevaluated other 59 patients who were helicobacter pylori free at six months after eradication, out of this 59 patients, 9 were helicobacter pylori positive and therefore our reinfection rate is 15.5% patient/year. Among the variables studied, only the effect of positive family history of Helicobacter pylori on the rate of recurrence of infection six months after successful eradication was significant, which had an odds ratio of 23.69, indicating its high effect on the recurrence of infection six months after successful eradication.

Conclusion: The percentage of recurrence of Helicobacter pylori in children in the northwest of the Iran, was similar to that of developing countries. Among the investigated factors, the history of infection in other family members in the recurrence of Helicobacter pylori with the same previous strain (relapse, after six months of Eradicating) played the most important role. Living in an H. pylori high prevalence area increases the annual risk of reinfection.

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GASTROENTEROLOGY - Peptic disease and helicobacter pylori

G-P-400

Gastric Mucosa - Associated Tissue (MALT) lymphoma due to Helicobacter pylori infection presents also in teenagers

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Objectives and Study: Helicobacter pylori (HP) infection in children is a frequent finding. Part of these patients may be asymptomatic and the rest with different gastrointestinal signs and symptoms including abdominal pain, vomiting, nausea, loss of appetite and also extra intestinal manifestations. In endoscopy the presenting signs are nodular gastritis, gastric & duodenal ulcers and gastric cancer. In histology with H& E staining we may find helicobacter pylori filaments on epithelial surface, acute and chronic gastritis, intestinal metaplasia changes, Mucosa-associated tissue (MALT) lymphoma cells and cancer cells. These proliferative changes are very rare in children.

We present three teenagers with recurrent upper abdominal pain which were diagnosed histologically with gastric MALT lymphoma treated against helicobacter pylori infection with disappearance of the bacteria and tumor during follow-up of 3-5 year.

Method: Three children aged 13-16 years old suffered from recurrent abdominal pain without vomiting, diarrhea, high grade temperature, sweeting or loss of weight. In endoscopy swelling antral mucosa was present with irregular surface occupying all prepyloric area and part of gastric corpus without nodular gastritis or gastric ulcers.

Histologic staining with H& E showed multiple HP elements on epithelial surface, large amount of lymphoma cells & lymphoepithelial lesions, positive for Kappa light chain staining and negative for Lamda light chain staining consistent for MALT lymphoma.

Patients were treated for 10 days with triple therapy (Amoxicillin, Clarithromycin and Omeprazole) with disappearance of HP in breath test in 2 patients and after second course with quarter drugs (Amoxicillin, Metronidazole, Clarithromycin, Omeprazole) for 14 days in the third one.

Repeated endoscopies and histologic findings were within normal limits during follow-up 3-5 years post first diagnosis.

Conclusion: MALT lymphoma must be diagnosed and treated also in teenagers.

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Cytokines in pediatric gastritis associated with helicobacter pylori

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Chronic gastritis (CG) is an actual problem because of it is wide spreading among children and adolescents and results of treatment are not always satisfactory.

Aim was to estimate role of cytokines in development of pediatric gastritis.

Materials and methods: 30 children with CG and 16 healthy ones aged 9-16 as a control group was examined. Serum cytokines were studied by ELISA (test system by “Cytokine”, St. Petersburg, Russia). Fibroesophagogastroduodenoscopy with biopsy was made. Morphological symptoms of CG were found. 18 patients had H.pylori-positive CG, 12 - H.pylori-negative CG. Serum H.pylori antibodies were studied. The median and interquartile interval (from 25 to 75 percentile) were determined. The groups were compared in pairs using the Kruskel-Wallis criterion. Statistically significant differences were considered when p< 0.05.

Results: The median concentration of IL1β in children with CG was 142 [128; 169] pg/ml and 4.6 times more than in the control group (p&LT; 0.001). IL2 level was 127 [101; 148] pg/ml - 4.5 times more than in the control group (p&LT; 0.001), TNFα concentration was 119 [104; 152] pg/ml - 5.9 times more than in the control (p&LT; 0.001), IFNα 132 [116; 162] pg/ml 6.1 times more than in the control (p&LT; 0.001). The data show normal level of IL4 28 [21; 37] pg/ml (comparing with control 24 [21; 32] pg/ml, p&LT; 0.05).

In patients with Helicobacter-associated CG, a higher content of IF-α was detected (147.83 vs. 80.8 in uninfected). Direct correlation was found between the level of H.pylori antibodies and the concentration of TNFα (r=+0.41; p&LT; 0.05) and reverse - between the level of H.pylori antibodies and IL4 (r=-0.35; p&LT; 0.05). Consequently, H. pylori stimulates the synthesis of pro-inflammatory cytokines. We used the ratio of proinflammatory cytokines to anti-inflammatory IL-4. The coefficients show a significant predominance of pro-inflammatory cytokines over IL-4. The coefficients were higher for Helicobacter-associated gastritis. The IL-2 / IL-4 ratio in infected patients was 10.53, and in helicobacter-negative forms 5.40. The coefficients for IF-α / IL-4 were 5.22 and 2.52 respectively. Consequently, H. pylori initiates a local inflammatory response. The first step in the activation of the immune response in CG is the enhanced production of cytokines, mainly proinflammatory, so determining their level can serve as a criterion for diagnosing the pathological process in children with CG.

Conclusion:
1. Pro-inflammatory cytokines IL1β, IL2, TNFα and IFNα were increased in pediatric CG.
2. Anti-inflammatory IL4 had normal level and it may be estimated as an unfavorable reaction.
3. Close correlation connection was found between cytokines concentration and H.pylori antibodies level.

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**Objectives and Study:** Many worldwide studies have shown no relation between recurrent abdominal pain (RAP), the characteristic manifestation of functional dyspepsia (FD), and chronic Helicobacter pylori (Hp) infection in children and adolescents in absence erosive/ulcerative lesions in the stomach or duodenum (EUSD). However, data regarding this dependency are mostly available for regions with low Hp prevalence.

**Methods:** 270 adolescents with RAP complaints aged 11-17, referred to a pediatric gastroenterology center (Krasnoyarsk, Siberia, Russia), were screened by Questionnaire on Pediatric Gastrointestinal Symptoms Rome III Version to diagnose pain related FD as well as Hp positivity (Hp antigen ELISA monoclonal test in stool (Immundiagnostik, Germany), Hp presence in antral biopsy (1 specimens) and anti-Hp-cagA antibodies in plasma (ELISA, Vector-Best, Russia). All adolescent were undergo upper endoscopy, in 74 were diagnosed EUSD. The calculation of Odds Ratio (OR) with confidence interval (CI) and two-sided Fisher’s exact test with Yates’ correction were used.

**Result:** The moderate positive association was detected between both pain related FD and EUSD groups and Hp presence according stool antigen test results (Table 1). Only EUSD group exhibited the strong positive association with anti-Hp-cagA antibodies presence (OR=4.0 (CI=2.21-7.25), p< 0.001).
**Table 1. Helicobacter pylori prevalence in adolescents with pain related functional dyspepsia (FD) and erosive/ulcerative lesions in the stomach or duodenum (EUSD)**

<table>
<thead>
<tr>
<th>Helicobacter pylori detection method</th>
<th>No pain related FD and/or EUSD</th>
<th>Pain related FD</th>
<th>EUSD</th>
<th>Odds Ratio (confidence interval), p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hp stool antigen test</strong></td>
<td>51.0% (73/143)</td>
<td>76.0% (19/25)</td>
<td>67.2% (39/58)</td>
<td>OR&lt;sub&gt;0.1&lt;/sub&gt;=3.04 (1.15-8.03), p=0.022 OR&lt;sub&gt;0.2&lt;/sub&gt;=1.97 (1.04-3.73), p=0.038</td>
</tr>
<tr>
<td><strong>Antral biopsy for Hp presence</strong></td>
<td>54.1% (66/122)</td>
<td>83.3% (20/24)</td>
<td>65.3% (47/72)</td>
<td>OR&lt;sub&gt;0.1&lt;/sub&gt;=4.24 (1.37-13.15), p=0.009 OR&lt;sub&gt;0.2&lt;/sub&gt;=1.60 (0.87-2.91), p=0.128</td>
</tr>
<tr>
<td><strong>Anti-Hp-CagA antibodies presence</strong></td>
<td>20.0% (33/165)</td>
<td>35.5% (11/31)</td>
<td>50.0% (37/74)</td>
<td>OR&lt;sub&gt;0.1&lt;/sub&gt;=7.2 (0.96-5.04), p=0.059 OR&lt;sub&gt;0.2&lt;/sub&gt;=4.0 (2.21-7.25), p=0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** We suppose that in adolescents with pain related FD the anti-*Hp-cagA* antibodies presence should be considered as an important additional indication for eradication therapy to prevent erosive/ulcerative lesions.
The epidemiological characteristics of helicobacter pylori infections in gastroduodenal pathologies in childhood

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Objectives and Study: To determine the frequency of H. pylori infections of patients applied to Çukurova University Medicine Faculty Pediatric Gastroenterology polyclinic with dyspeptic complaints and indicate the distribution of virulence factors, the importance of intrafamilial transmission, and also resistance to macrolide and quinolon group antibiotics by identifying epidemiological characteristics of them at the genotype level.

Methods: A total of 110 patients with dyspeptic complaints referred to hospital between 13 January 2015-1 December 2016 were included in the study. Of the cases, those with H. pylori positivity and dyspeptic complaint and 7 parents whose upper gastrointestinal system endoscopy was conducted by adult gastroenterology department were also involved in the study. H. pylori was searched by means of histopathological, culture and glmM-PCR methods. In the patients whose PCR was identified as positive, the determination of vacA, cagA and cagE genes was performed; in addition, E-test was performed to establish the resistance of clarithromycin and levofoxacin of H. pylori strains isolated in culture. A2142G and A2143G point mutations held responsible for clarithromycin resistance were identified with PCR-RFLP method. The effect of H. pylori strains on the clinics of cases was investigated and the impact of intrafamilial H. pylori transmission was evaluated.

Results: H. pylori was established as positive in 30 (27.3%) out of 110 pediatric patients. The average age of the cases was 12.2 ± 4.39 years (ranging from 3-18). 65.5% were female, 34.5% were male. In 40% of H. pylori positive patient samples vacAs1, in 56.6% vacAs2, in 36.7% cagA, in 23.3% cagE were positive. In 6.6% of the cases vacAs1+cagE association, in 16.6% vacAs1+cagA+cagE association and in 16.6% vacAs2+cagA association were determined. No significant relationship was identified between clinical findings and H. pylori strains in the study. Levofoxacin resistance was only observed in one (4.3%) of the patients that could produce H. pylori in the culture. In the patient involved, both genetic mutations of A2142G ve A2143G were found as positive. In 8 patients (34.7%), clarithromycin resistance was established. In all patients whose A2142G mutation was determined as positive and in and 55% those whose A2143G mutation was identified as positive, clarithromycin resistance was observed. H. pylori strains determined in the parents of pediatric patients involved in the study were determined as different from H. pylori strains in the children.

Conclusions: H. pylori infection was determined as positive in approximately one third of children with dyspeptic complaints. In children applying to hospital with dyspeptic complaints, it was observed that vacAs2 is the mostly seen genotype. Of the genetic mutations A2142G ve A2143G, even having at least one of them carries a potential for resistance to antibiotics. High resistance was identified for clarithromycin used in the standard triple treatment of H. pylori in children.

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Autoimmune gastritis in children: report of two girls with refractory iron deficiency anemia

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Objectives and Study: Autoimmune gastritis is a chronic inflammatory condition with destruction of parietal cells of the corpus and fundus of the stomach. It is rarely diagnosed in children. In adults the disease usually presents with pernicious anemia. The course of the disease; how to follow or how to monitor these children are not clear. Two girls, diagnosed autoimmune gastritis while investigating the cause of refractory iron deficiency anemia were reported.

Method: Descriptive, observational case-series (with two patients). Medical records of two patients diagnosed autoimmune gastritis at Sisli Hamidiye Etfal Education and Research hospital, department of pediatric gastroenterology were reported at a seven-year period.

Results: Two girls, aged 11 and 14 years old were referred to pediatric gastroenterology outpatient clinic, because of refractory iron deficiency anemia. Upper gastrointestinal system endoscopy revealed softening of gastric folds and histologic analysis of gastric and duodenal biopsies showed gastric atrophy in corpus mucosa and both of the biopsies showed micronodular intestinal metaplasia with chromogranin A an synaptophysin staining. Clinical characteristics were summarised at the table. The children were closely monitored and followed from the outpatient clinic with endoscopic evaluation and hematologic parameters.

Conclusion: This rare entity was presented with refractory iron deficiency anemia and at the follow up B12 and iron deficiency anemia are monitored and treated. As it is considered to be precancerous lesion close monitoring of these children is mandotory.

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)/Gender</td>
<td>11/Female</td>
<td>14/Female</td>
</tr>
<tr>
<td>History</td>
<td>Autoimmune Thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>-cell disease in the family history</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>Loss of appetite,fatigue</td>
<td></td>
</tr>
<tr>
<td>HB (gr/dL)/Ferritin (ng/mL)</td>
<td>8,9/0,5</td>
<td>9/18</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>362</td>
<td>175</td>
</tr>
<tr>
<td>Parietal cell antibody</td>
<td>(+) 1:100</td>
<td>(+) 1:320</td>
</tr>
<tr>
<td>Intrinsic factor antibody</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Gastrin (pg/ml)</td>
<td>500</td>
<td>920</td>
</tr>
</tbody>
</table>

[Data of the patients]

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Diagnostic relationship between Nodular Antral Gastritis and H. pylori infection on endoscopic examination

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Objectives and Study: Helicobacter pylori causes chronic active gastritis and may result in duodenal, and to a lesser extent gastric, ulcers. Persistent infection with H. pylori increases the risk of gastric cancer. Nodular antral gastritis (NAG) is defined as gastritis with endoscopic findings that include a nodular or diffuse miliary pattern of small elevations in gastric mucosa, observed mainly in the antrum and occasionally extending to the whole stomach body. Several studies were reported that the presence of antral nodularity is highly predictive of Helicobacter pylori (H. pylori) infection. The aim of our study was to confirm the role of antral nodularity in the diagnosis of H. pylori infection in children.

Method: This is a retrospective study of single center. The patients, who had NAG detected by upper gastrointestinal system endoscopy (UGSE) during 2012 to 2017, were investigated for H. pylori infection. H. pylori infection was defined as positive result with histopathological examination and/or urea breath test.

Results: During study period, 193 children were diagnosed as NAG by UGSE. Age range of patients was 4 to 18 years old. Female predominance was detected (72%; 139F/54M). Histopathological examination of antral gastric biopsies was performed to 169 of 193 patients and, H. pylori infection was detected in 76.9% (130/169). Whereas, urea breath test was performed to 140 of 193 patients and, H. pylori infection was detected in 81.4% (114/140). Both tests were positive in 34.1% of patients (66/193). Overall, H. pylori infection was detected in 91.7% of patients by histopathological examination or/and urea breath test (177/193).

Conclusion: Histopathological examination of biopsy materials is required experienced pathologist and certain amount of time, and have significant economic burden. And, urea breath test is not a harmless test, because it contains radioactive substance. So, if NAG can be evaluated properly by UGSE, H. pylori infection can be predictable. We think that, if NAG detected by UGSE, anti-H. pylori infection can be started without waiting for the biopsy or urea breath test results.
The impact of liver transplantation on plasma and CSF amino acids in patients with argininosuccinic aciduria

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Objectives and Study: The positive effect of liver transplantation (LT) in ASLD has been reported in a very few patients, allowing termination of low-protein diet, arginine supplementation and ammonia scavengers therapy. However, the impact of LT in improving amino acid abnormalities has not been well studied so far. In one child, it has been shown a reduction of ASA after LT, while data about changes of plasma citrulline concentrations are contrasting in the 2 children studied. Indeed, given the persistent inability to synthesize arginine extrahepatically, it is not known the long term impact of this persistent metabolic aberration, especially in CNS. Only two papers reports on CSF ASA in ASLD patients, but no data are available in transplanted patients.

Methods: As part of our LT assessment protocol in ALSD, amino acids were determined in plasma (71 samples) and CSF (8 samples) in 5 patients transplanted or listed for LT. Values are expressed as µmol/L. To compare data before and after OLT we used unpaired t-test.

Results: Mean ASA levels in plasma were significantly decreased by LT (445±45 vs 112±7; p<0.0001) and they correlated directly with ammonia levels (r: 0.66, p<0.001). Remarkably, in contrast to what found in plasma, CSF concentration of ASA before and after LT did not differ, with persistence of a strong elevation (476±42 vs 407±84). Glutamine (848±30 vs 711±13) and citrulline (205±9 vs 163±6 µmol/L) concentrations in plasma also significantly decreased after LT (p<0.0001), with persistence of mildly elevated levels in CSF (glutamine 680±24 vs 701±49, normal < 590; citrulline 22±2 vs 16±3; normal < 6). 

Conclusion: We demonstrate that LT has no impact on ASA levels in CSF, implying that metabolic alteration still exist in the CNS compartment beyond hepatic transplant, possibly contributing to the neurologic outcome in ASLD patients after LT.

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Effects of synbiotics on non-alcoholic fatty liver disease as a complementary / supportive treatment

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²Ordu University Educational Research Hospital, Ordu, Turkey
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⁴Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

Objectives and Study: Non-alcoholic fatty liver disease (NAFLD), defined by excess fat accumulation in the liver without a history of excessive alcohol intake, is the most common causes of chronic liver disease. Dietary factors and intestinal bacteria play an important role in the rapidly increasing incidence of obesity and its associated conditions, such as steatosis and insulin resistance. In the current study, we evaluated the effect of synbiotics on diet-induced NAFLD and weight gain in rats.

Method: Male Wistar Albino rats were fed a high sugar and high fat diet for 60 days. After 8 weeks, rats are randomly allocated in two groups (at least n=6) as follows: control group, receiving standard diet; and synbiotic groups, receiving standard diet and synbiotic for 15 days. Synbiotic consisted of Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium animalis ssp lactis B94 and fructooligosaccharide (1X10⁹ CFU/day). Body weight, ALT and AST levels were measured on 0, 60 and 75 days. On day 60, the presence of hepatosteatosis was confirmed by liver ultrasonography. After 75 days, rats were sacrificed under anaesthesia, with liver tissue extracted for histopathological analyzes.

Results: At baseline and day 60, there was no significant difference in body weight, ALT and AST levels between groups, however in day 75, there was a significant decreases in ALT activity, and body weight in the synbiotic group compared to the control group but not in AST levels. Histopathological analyzes showed that the severity of hepatosteatosis was more pronounced in the non-synbiotic control group (image 1).

Conclusion: Overall, our data indicate that the Lactobacillus and Bifidobacterium based synbiotic mixture is effective in reducing the hepatosteatosis and weight gain with high fat and sugar intake, suggesting its possible therapeutic/preventive utilization for NAFLD.

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**Determination of the efficacy of a gene therapy approach for the treatment of Crigler-Najjar in the UGT1 KO mouse model**

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**Objectives and Study:** Crigler-Najjar syndrome (CN) is an autosomal recessive disorder caused by mutations in the uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) enzyme, resulting in partial or complete absence of activity. As UGT1A1 is responsible for bilirubin metabolism, CN is characterized by hyperbilirubinemia and jaundice. A gene therapy approach for the treatment of CN was evaluated in an animal model of CN, the UGT1 knockout (KO) mouse, for potential toxicity and to estimate the minimally effective dose (MED) of a clinical candidate vector, which uses the adeno-associated viral (AAV) vector capsid 8 to express the human version of UGT1A1.

**Methods:** UGT1 KO mice display lethal hyperbilirubinemia in the immediate postnatal period. Modeling of clinical phototherapy for 12 hours per day from birth to 21 days of age increases survival and allows gene therapy administration to be delayed until after the most proliferative phase of liver development. Adult phototherapy-rescued UGT1 KO mice have serum total bilirubin levels of 9.1 ± 3.0 mg/dl and were administered with one of four doses of AAV8-TBG-hUGT1A1 (AT342), ranging from $2.5 \times 10^{10}$ to $2.5 \times 10^{13}$ genome copies (GC)/kg with an additional group of mice receiving vehicle only as a control. Mice were bled biweekly to evaluate serum total bilirubin levels and liver transaminases. Animals were sacrificed on day 56 post vector administration and tissues were harvested for a comprehensive histopathological examination.

**Results:** There were no apparent clinical sequelae following either administration of the vector or vehicle control. Abnormalities in clinical pathology were restricted to dose-dependent elevations in liver transaminases. ALT elevations ranged from 1-9.1x baseline levels and were primarily found in male UGT1 KO mice at day 28 following administration of the highest dose of vector ($2.5 \times 10^{10}$GC/kg). While there were histopathological findings in male mice administered with the control article, the majority of the findings were in male mice administered with the highest dose of vector, with all findings graded as minimal to mild. A complete reversal of total bilirubin levels to wild type levels of 0.1-0.3 mg/dl occurred at doses $>2.5 \times 10^{10}$ GC/kg in male mice and $>2.5 \times 10^{11}$ GC/kg in female mice. At the lowest vector dose evaluated ($2.5 \times 10^{10}$ GC/kg) a transient effect on total bilirubin levels occurred in male mice, while there was no deviation from baseline values in female mice.

**Conclusion:** The MED for sustained and complete normalization of total bilirubin levels in the mouse model of CN following administration of AT342 is equal to $2.5 \times 10^{11}$ GC/kg. These studies support the ongoing clinical investigation of AT342 for the treatment of Crigler-Najjar syndrome. Aspects of these studies have been repeated with a clinical process comparable preparation of AT342 with equivalent results.

**Disclosure of interest:** J.M. Wilson is an advisor to REGENXBIO, Ultragenyx Gene Therapy, and Solid Gene Therapy, and is a founder of, holds equity in, and has a sponsored research agreement with REGENXBIO; in addition, he is a consultant to several biopharmaceutical companies and is an inventor on patents licensed to various biopharmaceutical companies. J. Gray is employee of Audentes Therapeutics.
Autoantibodies against Huntingtin-interacting protein 1-related protein: A potential new diagnostic tool for paediatric autoimmune hepatitis

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Objectives and Study: Autoantibodies are key parameters in the diagnostic of autoimmune hepatitis (AIH). However, conventional autoantibodies such as anti-nuclear (ANA), anti-smooth muscle (SMA) and antibodies against soluble liver antigen (SLA) either lack high sensitivity or high specificity to distinguish AIH from non-AIH liver disease. Therefore we screened for alternative autoantibodies.

Method: Antibodies against Huntingtin-interacting protein 1-related protein (HIP1R) were identified via a protein macroarray in adult patients with AIH. Next, antibodies against a HIP1R fragment, measured with an ELISA, were compared to conventional autoantibodies, measured by immunofluorescence with age dependent cut-offs based on international guidelines, in two independent retrospective cohorts from two centers (Hannover=training cohort; London=validation cohort). The cohorts included children with untreated paediatric AIH (N=48 and 19), non-AIH liver disease (N=48 and 21; primary sclerosing cholangitis, toxic hepatitis, non-alcoholic fatty liver disease, cryptogenic chronic hepatitis, alpha-1-antitrypsin deficiency and others) or without liver and autoimmune diseases (N= 35).

Results: Children with untreated paediatric AIH (pAIH) had higher anti-HIP1R IgG antibody concentrations as compared to pAIH overlap syndromes, non-AIH liver disease (nAIH-LD) or children without liver disease (p&LT; 0.001 for all comparisons). With the receiver operating characteristic the optimal cut-off for the distinction between untreated pAIH and nAIH-LD was identified with 43.3 arbitrary units. For the identification of untreated pAIH versus nAIH-LD anti-HIP1R antibodies with cut-off at 43.3 arbitrary units showed following performance: AUC: 0.95 (confidence interval: 0.90-0.99); Odds ratio: 87.7; 21.3-362.4 and achieved a significantly higher sensitivity (0.94; 0.82-0.98) and negative predictive value (0.93; 0.80-0.98) with the highest overall accuracy (0.90; 0.80-0.98) compared to ANA (0.81; 0.72-0.88), SMA (0.72; 0.62-0.80) and SLA (0.48; 0.37-0.59) antibodies in the training cohort from Hannover/Germany (48 pAIH patients, 48 nAIH-CLD patients). The specificity (0.85; 0.72-0.94) and positive predictive value (0.87; 0.74-0.94) from anti-HIP1R antibodies were not significantly different from ANA and SMA in this cohort. In the external validation cohort from London/UK (19 pAIH patients, 21 nAIH-LD patients) untreated pAIH had a lower anti-HIP1R antibody concentrations but still achieved the highest OR (34.3; 3.8-313.8) and overall accuracy (0.80; 0.64-0.90) compared to ANA and SMA. Due to the smaller sample number in the validation cohort only the specificity of anti-HIP1R (0.95; 0.74-1.00) was significantly higher than for SMA (p&LT; 0.05).

Conclusion: Anti-HIP1R autoantibodies may add a novel tool for the diagnostic work up in pAIH. They even seem to be superior to conventional autoantibodies (ANA, SMA, SLA) by a better clinical prediction of AIH and by a simpler and less expensive test approach (ELISA instead of immunofluorescence).

Disclosure of interest: Richard Taubert and Elmar Jaeckel registered a patent for anti-HIP1R antibodies.

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HEPATOLOGY - General Hepatology

H-O-005

Infantile hepatic haemangioendothelioma: clinical features and predictors of outcome in a large cohort of patients

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2 Spedali Civili di Brescia, Brescia, Italy

Objectives and Study: Hepatic haemangioendothelioma (HHE), although rare, is the most common benign liver tumour in children, with onset in the first few months of life. The management of the lesion may be particularly challenging when it extends to most liver sectors, causing high cardiac output and cardiovascular decompensation. The management of HHE is controversial: the current armamentarium available includes medical treatments, interventional radiology and surgery, but evidence to choose each one of them is lacking. We aimed to review a large cohort of children who presented to our centres with HHE in the last 20 years, to find predictors of poor outcome and critically appraise the best treatment choice in different presentations.

Method: We retrospectively reviewed the files of patients diagnosed with HHE, and collected age at presentation, clinical features, extension of the disease and histology when available, diagnostic process, management and outcome. All patients underwent liver ultrasound, CT scan and/or MRI, echocardiography. The tumour was classified as focal in presence of ≤ 4 lesions, multifocal if ≥ 4 lesions, diffuse if ≥ 20 lesions.

Results: 27 patients (5 males, 22 females) of a median age of 13 days (1-1530) presented with hepatomegaly (24/27), cardiac failure (10/27), cutaneous haemangiomas (8/27), fever and anaemia (6/27 each), vomiting (5/27), splenomegaly (4/27), jaundice (3/27), failure to thrive (3/27). Four patients had hypothyroidism. The lesion was focal, multifocal, or diffuse in 9 patients of each group. Histology, available in 8, showed type I lesion in 3/8 (all focal lesions) and type II in 5 (all diffuse lesions), of which 2/5 had foci of angiosarcoma. Focal lesions were managed with medical treatment (3/9), embolization (2/9), resection (3/9), conservatively (1/9); multifocal lesions with medical treatment (3/9), embolization (1/9), conservatively (5/9); diffuse lesions with medical treatment (2/9), embolization (5/9), liver transplantation (2/9). After a median follow up of 16 months (30 days-11 years), 23/27 (85%) patients survived with disease remission. Independent predictors of mortality were a diffuse lesion (4/4), cardiac failure at diagnosis (4/4), a type II histology (4/4); age older than 6 months at diagnosis (3/4)(all p≤LT; 0.01).

Conclusion: Some 85% of patients with HHE can be managed successfully with a combination of medical, radiological and surgical treatments. Patients with diffuse lesions, late presentation, cardiac failure and type II histology have a poor outcome, and should be approached more aggressively to prevent major complications and death.
Liver disease related to alpha1-antitrypsin deficiency in French children: the DEFI-ALPHA cohort

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Objectives and Study: The DEFI-ALPHA cohort included French children with alpha-1 antitrypsin (AAT) deficiency, irrespective of phenotype, in order to identify prognostic factors for liver disease.

Method: A multicenter study was conducted, retrospective then prospective from 2010, including all children with AAT less than 0.8 g/L, born in France since 1989. Clinical and biological data were collected. Liver disease severity was classified as: “severe” (portal hypertension - PHT, liver failure, liver transplantation, or death); “moderate” (persistent abnormal liver biology without PHT); and “mild/none” (normal liver function and native liver). Prognostic factors for severe liver disease were evaluated using a Cox semi-parametric model.

Results: In December 2017, 162 patients were included, from 19 centres. Genotypes were PIZZ in 80%, PISZ in 8%, other in 12%. Diagnosis was made before two months of age in 52%, by neonatal cholestasis. Mean ±SD follow-up was 5.3 ± 2.3 years. Three-quarters of patients had abnormal liver biology at diagnosis. Among them, 28 (17%) developed severe liver disease (mean age 2.6 years, range: 0-11.6), and 16% were moderate, with persistent abnormal liver biology. Genotypes of severe patients were PIZZ in 25 (89%), PISZ in 2, PIMlikeZ in 1. Sixteen children underwent liver transplantation. One child with comorbidities died at 3 years of age from infection. Neonatal cholestasis was significantly associated with severe liver disease (p=0.007).

Conclusion: AAT deficiency is a frequent cause of liver disease in childhood, sometimes with cirrhosis, probably under diagnosed. AAT deficient patients presenting with neonatal cholestasis were likely to develop severe liver disease. The presence of PHT in non-homozygous ZZ patients highlights the possible severity of other compound heterozygote genotypes such as PISZ, and M variants, and that should be diagnosed and followed-up in adulthood. The threshold for AAT deficiency detection should probably be increased to avoid missing such genotypes. Ongoing genetic studies should identify genetic polymorphisms involved in the development of liver complications.

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Clinicopathological study in 80 patients with Biliary atresia treated by liver transplantation with and without prior Kasai portoenterostomy

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Objectives: Biliary atresia (BA) is a non-hereditary disease, unknown in etiology and affecting 1/18,000 births in Europe. Kasai portoenterostomy (KPE) is performed immediately after diagnosis. Depending on the patient's condition, liver transplantation (LT) may be needed. Pathological features in the explant liver could be a combination between original features (BA itself) and secondary features (influence of KPE). For instance, a perihilar benign hepatic nodule reported in Asian long surviving BA cohorts, is considered as secondary to the KPE. Our aim was to further enhance understanding of BA pathology by comparing clinicopathological-and macroscopical features in 80 BA LT patients with and without previous KPE.

Material and methods: We investigated 80 BA patients who underwent LT (median age at LT: 2.5 years, 4 months to 32 years) at Saint-Luc Hospitals between 2009 and 2017. Clinical information was obtained by patient's file. Macro- and microscopical aspects were reviewed by liver-specialized pathologist.

Results: Forty-eight (60%) out of 80 BA patients underwent KPE before LT. Post-KPE patients were significantly earlier diagnosed (P=0.001), older age at the LT (p=0.024), a longer time between BA diagnosis and LT (p=0.001), and showed a lower total bilirubin level (p=0.031), a higher albumin level (p=0.003), cholangitis (p=0.003), and severe portal hypertension (p=0.035) compared to non-Kasai group. Pathologically, non-KPE group showed significantly higher occurrence of extrahepatic bile ducts (P=0.013), bilirubinostasis (P=0.048), and giant cell transformation (P=0.041) compared to KPE-group. Macroscopically, 80 BA were classified into three groups, biliary plug group (n=37, 46.2%), non-biliary plug group (N=35, 43.8 %), and large nodular group (n=8, 10%). Bile plug group was defined as a case showing biliary plugs in perihilar location. Fifteen (40.5%) out of 37 bile plug group cases showed biloma as well bile plugs. Non-biliary plug group was defined as a case without biliary plug or biloma. Finally, large nodular group was defined as a case showing a large nodular lesion. Large nodules measured between 3.5 cm and 10 cm and their locations were always near perihilar area. Large nodular group all had post-KPE status and showed significantly older age at the time of LT, a longer time between time of diagnosis and time of LT, higher prevalence of left liver graft, and lower Total Bilirubin level, compared to the other two groups. Pathologically, a large nodular area showed preserved liver architecture, less fibrosis and less hepatocellular damage and inflammation, compared to non-nodular area. There was no sign of malignancy in the nodules. Large nodular group showed a significantly less bilirubinostasis (p=0.001), less ductal plate malformation (P=0.005) and less extravasation of bile (P=0.001), compared to the other groups.

Conclusion: Explant livers of BA patients with previous KPE more frequently showed cholangitis and/or severe portal hypertension, and better liver function than without KPE. Our data confirmed that a benign hilar nodule was seen in long survived post-KPE BA patients with distinct clinicopathological features. Based on these aspects, possible pathogenesis of the large nodule could be better biliary drainage of the perihilar liver due to KPE.
Serum concentration of ceramides in obese children with nonalcoholic fatty liver disease

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Objectives and Study: Ectopic hepatic lipid accumulation is closely related to the development of insulin resistance, which is regarded as one of the most significant risk factors of non-alcoholic fatty liver disease (NAFLD). Ceramides are the main mediators of lipid-induced hepatic insulin resistance. Therefore, the aim of the study was to evaluate the serum ceramides concentration in obese children with NAFLD.

Method: The prospective study included 80 obese children (aged 7-17 years, median 12 years) admitted to our Department to diagnose initially suspected liver disease. Patients with viral hepatitis (HCV, HBV, CMV), autoimmune (AIH), toxic and metabolic (Wilson's disease, alfa-1-antitrypsin deficiency) liver diseases were excluded. NAFLD was diagnosed in children with liver steatosis in ultrasound as well as elevated alanine aminotransferase (ALT) serum activity. The degree of liver steatosis (graded according to Saverymuttu scale) was determined by ultrasonography. Advanced steatosis was defined as a score >1. The total intrahepatic lipid content (TILC) was assessed by magnetic resonance proton spectroscopy (1H-MRS). Fasting serum concentration of ceramides was measured in 62 children.

Results: NAFLD was diagnosed in 31 children. Significant, positive correlation was found between total serum concentration of ceramides and insulin (r=0.3, p=0.02) and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (r=0.28, p=0.03). Total ceramide concentration as well as myristic, palmitic, palmitoleic, stearic, oleic, behenic and lignoceric ceramide concentrations were significantly higher (p=0.004, p=0.003, p=0.007, p&LT; 0.001, p=0.035, p=0.008, p=0.003, p=0.006, respectively) in children with NAFLD compared to controls (n=14). Moreover, children with NAFLD had significantly higher activity of ALT (p&LT; 0.001) and gamma glutamyltransferase (GGT) (p&LT; 0.001), HOMA-IR (p=0.04), BMI (p=0.046), waist circumference (p=0.01) steatosis grade in ultrasound (p&LT; 0.001) and TILC in 1H-MRS (p&LT; 0.001) compared to children without NAFLD. We did not find significant differences in ceramides concentrations between children with mild (grade 1) and advanced liver steatosis in ultrasonography (grade 2-3).

Conclusion: Elevated ceramides concentrations and their significant correlation with insulin resistance suggest their potential role in development of NAFLD in obese patients.

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A metabolomic salivary signature of pediatric obesity related liver disease.

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Objectives and Study: Pediatric obesity-related non alcoholic fatty liver diseases (NAFLD) is an increasingly important condition with a still incompletely understood pathogenesis, and poor efficacious treatment and/or monitoring options. Here we investigated its salivary metabolomic signature, which is hitherto uncharacterized.

Method: We recruited for our pilot case-control study 41 subjects [23 obese and 18 normal weight (NW) healthy controls] characterized on the basis of medical history, clinical, anthropometric, and laboratory data. Liver involvement, defined on the basis of ultrasonographic liver brightness, allowed to allocate patients into 2 groups: obese with ([St+], n=15) and without ([St-], n=8) hepatic steatosis. A morning saliva sample from each subject was collected by Salivette® and analyzed by GC-MS. Partial Least Squares Discriminant Analysis (PLS-DA) was performed to improve the separation between groups, by rotating Principal Components Analysis for achieving a maximum separation among classes, and understanding which variables carry class separating information.

Results: A well-defined differentiation of patients with and without hepatic steatosis and controls was obtained by using the model with 21.3% of the total variance explained in the first two latent components. Thirteen variables important in projection (VIPs) were identified by PLS-DA setting the VIP score=2 as a cut-off value. The 11 VIPs were:
A. Hydroxybutyric acid, malic acid, methylmaleic acid, maltose, xylose, all having the higher mean concentrations in control group;
B. Lauric acid and Butanendiol with higher concentrations in overweight/obese
C. Palmitic acid, urea, N-acetyl galactosamine, myristic acid, all having the higher mean concentration in overweight/obese with steatosis group.

The Table illustrates the individual VIP metabolites fold changes in [St-] and [St+] vs.controls (*=p<0.05, **=p< 0.01, ***=p< 0.001).
<table>
<thead>
<tr>
<th>Variables important in projection (VIPs)</th>
<th>Controls</th>
<th>[St-]</th>
<th>[St+]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased in Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malic acid</td>
<td>0.178254</td>
<td>-0.98</td>
<td>-0.98</td>
</tr>
<tr>
<td>Methylmaleic acid</td>
<td>0.013756</td>
<td>-0.72</td>
<td>-0.24</td>
</tr>
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<td>Maltose / Xylose</td>
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<td>-0.25/-0.34</td>
</tr>
<tr>
<td>Hydroxybuthyric acid</td>
<td>0.006976</td>
<td>-0.62*</td>
<td>-0.14</td>
</tr>
<tr>
<td>Increased in Obese [St -]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butanendiol / Lauric acid</td>
<td>0.000700 / 0.000610</td>
<td>2.79/ 3.35</td>
<td>6.16**/ 7.21**</td>
</tr>
<tr>
<td>Increased in Obese [St +]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmitic acid</td>
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<td>4.46***</td>
<td>8.06**</td>
</tr>
<tr>
<td>Myristic acid</td>
<td>0.000921</td>
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<td>7.58*</td>
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<td>Urea</td>
<td>0.000936</td>
<td>4.15**</td>
<td>7.65**</td>
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<tr>
<td>N-acetyl galactosamine</td>
<td>0.000884</td>
<td>3.72**</td>
<td>7.60*</td>
</tr>
</tbody>
</table>

[Table 1. Individual VIP metabolites fold changes.]

**Conclusion:** Pediatric obesity and its related liver disease appear having distinct salivary metabolomic signatures. The difference emerges especially from metabolites involved in energy, amino and organic acid metabolism, and in intestinal bacteria metabolism which reflect diets, fatty acid synthase pathways, and the strict interaction between microbiota and intestinal mucins. This piece of information expands the current understanding of NAFLD pathogenesis, potentially translating into future better targeted monitoring and/or treatment strategies.
Background and aims: Biliary atresia (BA) is a fibrotic disease of unknown etiology affecting the extrahepatic bile ducts (EHBDs) of newborns. The isoflavonoid biliatresone, which causes rapid decreases in glutathione (GSH), leads to a BA-like disease in newborn livestock and larval zebrafish as well as to EHBD obstruction in EHBD explants of a neonatal mouse model. As biliatresone represents a new model of BA, our goal was to understand the pathway of cholangiocyte injury. We have previously shown that biliatresone decreases GSH and decreasing GSH phenocopies biliatresone effect. We aimed to further understand the molecular mechanisms involving EHBD injury and the role of decreased GSH in the pathway.

Methods: We investigated molecular pathways by treating cholangiocytes in culture with biliatresone and Buthionine Sulfoxamide (BSO) to decrease GSH or DMSO. We then performed real time PCR, and immunofluorescence staining of cholangiocyte culture in different time points. Cholangiocyte organoids with open lumens were generated by growth in 3D culture and plasmids were used for overexpressing proteins.

Results: In a 3D model of cholangiocyte organoids, biliatresone caused an increase in Rhou and Hey2 expression. Both overexpression of Rhou and Hey2 resulted in lumen obstruction of cholangiocyte organoids. Both biliatresone and BSO caused an increased expression of Rhou and Hey2 after 3 hours of treatment, measured by immunofluorescence stain intensity. Both biliatresone and BSO increased Rhou expression by RT-PCR after 24 hours of treatment.

Conclusion: The molecular pathway of biliatresone toxicity includes decreases in GSH and increase in Rhou and Hey2. Decrease in GSH likely plays a central and possibly primary role in cholangiocyte injury. This is a potential cause of lumen obstruction, in vivo, that may be of importance in BA pathophysiology.
MicroRNA-29a mitigation of toll like receptor 2 and 4 signaling and alleviation obstructive jaundice-induced fibrosis in mice

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Objectives and Study: Continuous liver damage caused by cholestasis and hepatitis cause liver fibrosis. We have previously demonstrated that microRNA-29a (miR-29a) protects against liver fibrosis. Toll-like receptor (TLR2) 2 and TLR4 are the pattern recognition receptor of bacterial lipoprotein and lipopolysaccharide which are associated with activation of hepatic stellate cells and liver fibrosis. The aim of this study is to characterize the biological influence of miR-29a on TLR2 and TLR4 signaling in injured livers with bile duct ligation (BDL).

Method: We performed BDL on miR-29a transgenic mice (miR-29aTg) and wild-type mice to induce cholestatic liver injury. Primary HSCs were transfected with miR-29a mimic and inhibitor.

Results: Compared to the wild-type mice, the BDL demonstrated significant α-smooth muscle actin fibrotic matrix formation and hepatic high mobility group box-1 expression. In the miR-29aTg mice was significantly reduced. In addition, miR-29a overexpression reduced the BDL exaggeration of TLR2, TLR4, and MyD88, as well as proinflammatory cytokines, IL-1β, MCP-1, TGF-β and TNF-α. In vitro, miR-29a mimic transfection lowered α-SMA, TLR2 and TLR4 expressions in HSCs.

Conclusion: This study provides new molecular insight into the miR-29a inhibition of TLR2 and TLR4 that slows the progression of cholestatic liver deterioration.
HEPATOLOGY - General Hepatology

H-O-012

The correlation between histopathologic steatosis/fibrosis and various non-invasive imaging and blood fibrosis indicators of overweight and obese children

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Objectives and Study: Non-Alcoholic Fatty Liver Disease (NAFLD) has become the most common cause of chronic liver disease in children with the increasing frequency of worldwide obesity. NAFLD includes a spectrum ranging from benign hepatosteatosis to more serious steatohepatitis, and may evolve to cirrhosis. The current gold standard for the diagnosis and grading of NAFLD is a liver biopsy. Non-invasive procedures such as ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI) are available for the diagnosis of NAFLD, hepatic fibrosis and steatosis cannot be evaluated simultaneously by these methods. The aim of the study is to compare between the gold standard technique, namely liver biopsy and various non-invasive imaging methods and diagnostic biomarkers of liver fibrosis in overweight and obese children.

Method: Overweight or obese children between 8-18 years of age whose ultrasonographic findings and aminotransferase levels were compatible with NAFLD, underwent a diagnostic liver biopsy were recruited for this study. All of the patients were evaluated by using transient elastography (FibroScan) and controlled attenuation parameter (CAP) to investigate fibrosis and hepatosteatosis 1 to 4 weeks after the liver biopsy. APRI score was calculated in each patient, and magnetic resonance spectroscopy (MRS) was also carried out within a month of the liver biopsy.

Results: The mean age of the study group was 13.0±2.6 years and 68.8% of patients were male. The mean weight for height (WFH) ratio was 151.9±23.8% in this cohort. Five of 48 patients were overweight and 43 of them were obese according to body mass index (BMI) percentile, all patients were obese according to WFH ratio. Histopathologic evaluation of the liver biopsies revealed grade I steatosis in 27.1%, grade II steatosis in 16.7%, and grade III steatosis in 56.2% of the patients. Fibrosis was detected in nearly 60% of the patients with various degrees of hepatosteatosis (grade I-II-III fibrosis in 35.4%, 16.7% and 8.3% of patients, respectively). CAP assessment of hepatic steatosis in children was significantly correlated with the gold standard technique, namely histopathology in this group (p=0.01). Serum AST, ALT and GGT levels were significantly higher in patients with moderate to severe fibrosis compared to those having mild fibrosis or no fibrosis at all (p< 0.01). The mean APRI score of the patients with fibrosis was significantly higher than the patients without fibrosis (p=0.008, sensitivity 69.0%, specificity 73.7%, PPV 80%, NPV 60.9%). Moreover, APRI score was successful for discriminating between mild and severe fibrosis as well (p=0.001). FibroScan was successful for detecting fibrosis in patients with NAFLD, however it was not helpful in differentiating the grade of fibrosis. The grade of hepatosteatosis, detected by MRS was strongly correlated with the liver biopsy.

Conclusion: CAP and MRS can be used to detect the degree of hepatosteatosis in obese/overweight children. The FibroScan reliably revealed liver fibrosis, but the method is not sensitive enough to identify the degree of fibrosis. APRI score on the other hand was good at both detecting and grading fibrosis.
The role of N-acetylcysteine in preventing hepatic injury associated with systemic oxidative stress after extracorporeal shock wave treatment

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Objectives and Study: Systemic oxidative stress may produce detrimental consequences for several organs involving particularly liver. Aim of the study was to investigate histopathological changes in liver tissues due to the increased systemic oxidative stress associated with rat extracorporeal shock wave lithotripsy (SWL) model and to document the consequences of N-acetylcysteine (NAC) injection.

Method: In this experimental SWL model, 18 rats from a previous study were randomly assigned into three groups. Control group had no intervention. Second group underwent SWL treatment with intraperitoneal saline injection. Third group had also SWL with intraperitoneal NAC. Last group was divided into short-term and long-term. Hepatectomy was performed for histopathological examinations. Histopathological alterations were evaluated by light microscopy. Immunohistological staining for p53 and myeloperoxidase was also applied.

Results: Blood samples had revealed a significant increase in plasma oxidative stress index (OSI) by measuring plasma total antioxidant status (TAS) and total oxidant status (TOS) as in the initial trial. In this part, SWL associated systemic oxidative response affected liver tissues. Particularly, sinusoidal dilation was remarkably observed in rats with significantly high OSI values (p =0.043). Sinusoidal dilation was significantly protected in the long term NAC group. Similarly, periportal necrosis significantly increased in rats with high OSI values (p=0.033). Particularly p53 positivity was also remarkable in rats with systemic oxidative stress (p=0.049). NAC improved all these alterations including p53 staining.

Conclusion: We observed that SWL induced systemic oxidative stress cause histological alterations in liver tissues as sinusoidal dilation and periportal necrosis. Increased p53 and myeloperoxidase staining as markers of oxidative damage were also detected. NAC may protect from these histological and ultra-structural alterations related with oxidative stress.

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Portal infiltrate in protocol liver biopsies is associated with histological phenotypes and donor specific antibodies

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Objectives and Study: The cellular infiltrate in protocol liver biopsies (PB) following pediatric liver transplantation (pLT) remains mostly uncharacterized. Our aims were to define cell types and distribution in protocol liver biopsies, and to analyze possible associations with serum donor specific antibody (DSA) profile.

Method: All PB performed in children transplanted since 1989 were collected and reviewed. PB were defined as biopsies performed in patients with ALT and gGT < 50 U/l, at least one year after transplantation. PB were analyzed for fibrosis and inflammation and categorized into four phenotypes: normal, fibrosis only, inflammation only, inflammation with fibrosis. Tissue underwent immunostaining for CD3, CD4, CD8, CD68, CD20, MUM1 and FoxP3 expression respectively. Portal tracts and lobules were analyzed by counting number of cells of each type per 1000 micrometer² using NIS-Element v4.2. DSA and C1q binding activity were quantified using Luminex technology.

Results: Forty four (44) patients underwent one PB between 2000 and 2015. Eleven percent (11.4%) of PB displayed normal histology, 13.6% fibrosis only, 34.1% inflammation only and 40.9% inflammation & fibrosis. The main cell types in the portal tracts were CD3+ and CD68+ cells. De novo DSA were present in 62.8% of patient at PB, 1/27 had class I and all had class II de novo DSA. In the presence of inflammation & fibrosis, portal tracts were enriched in CD3+, CD20+ (figure 1). Inflammation PB displayed significantly fewer CD68+ than fibrosis PB. Similar trend for inflammation & fibrosis PB versus fibrosis PB. Inflammation & fibrosis PB were associated with the presence of de novo DSA and, number of de novo DSA in comparison to other phenotypes. De novo DSA were associated with enriched CD3+, CD4+, CD8+ and CD20+ portal infiltrate.

Figure 1:
Conclusion: In the clinically quiescent liver allograft of patients transplanted as children, CD3+ and CD68+ cells are the prevalent cell-types. In the presence of inflammation, cellular diversity and density changes to include more CD3+, CD20+ and fewer CD68+ cells. This coincides with the presence and number of de novo DSA and their C1q-binding capacity in peripheral blood. How these cellular and humoral actors interact is unclear, but peripheral DSA may be a marker of ongoing cellular signaling in the seemingly quiescent allograft.

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The natural course of FIC1 deficiency and BSEP deficiency: initial results from the NAPPED-consortium (NAatural course and progonosis of PFIC and effect of biliary diversion)


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24Toronto Center for Liver Diseases, Toronto, Canada

Objectives and Study: Severe deficiency of FIC1 (FIC1-def) or of BSEP (BSEP-def), due to mutations in the ATP8B1 and ABCB11 gene, respectively, are responsible for progressive familial intrahepatic cholestasis type 1 and 2. Because of impaired biliary bile salt secretion, patients typically present with pruritus and jaundice in early childhood. Patients may benefit from ursodeoxycholic acid (UDCA) or from surgical diversion (SBD) techniques. However, many patients need liver transplantation at child age. To better understand the nature of these diseases and the efficacy of interventions, we have set up an extensive international consortium, “NAPPED”.

Method: Herewith we present the retrospective follow up data from NAPPED on individual patients from 22 European and Asian centres who were either homozygous or compound heterozygous for disease associated mutations in ATP8B1 or ABCB11. Within the group of BSEP-def patients, we compared the severity of the mutations: mild (at least one D482G or E297G mutation), medium (at least one missense mutation, but not D482 or E297G) or severe (nonsense, frameshift, in/del/indel or splice site mutation). We used time-dependent Cox regression for native liver survival (NLS), adjusted for gender and birth year, in patients that had undergone SBD (SBD+) or not (SBD-). Continuous variables are expressed as median [range].

Results: We included 42 FIC1-def and 184 BSEP-def homozygous or compound heterozygous patients. Age at first visit in specialized centre was 6 months [0-201] in FIC1-def and 9 months [0-195] in BSEP-def. Use of UDCA prior to first visit was 33% in FIC1-def and 47% in BSEP-def patients. Age
at last follow up was 69 months [3-334] in FIC1-def and 62 months [1-487] in BSEP-def. SBD rates at five/ten years of age were 33/39% in FIC1-def and 28/35% in BSEP-def patients. Five/ten-year NLS was 73/51% in FIC1-def and 61/46% in BSEP-def patients. NLS in FIC1-def patients did not differ significantly between the SBD+ and SBD- groups. Before the age of five/ten years, 27/49% of FIC1-def and 36/52% of BSEP-def patients had been transplanted. Hepatocellular carcinoma was not seen in FIC1-def, but in 10% of BSEP-def patients (21% (6/28) in severe, 12% (7/60) in medium and 2% (1/48) in mild BSEP-def; P=.006). Pre-transplant mortality was 2% in FIC1-def and 5% in BSEP-def patients, and the observed NLS at 18 years was 51% and 33%, respectively.

SBD rates with age decreased significantly between patients with mild (n=64), medium (n=87) or severe (n=33) BSEP-def mutations, illustrated by the percentage of patients with SBD at age 10 years: 57%, 21%, and 14%, resp. (P< .001). Similarly, NLS with age decreased significantly in the order mild, medium and severe BSEP-def mutations (10yrs percentage: 60%, 37%, and 32%, resp.; P< .001).

Upon combining medium and mild BSEP-def patients, SBD+ was associated with a significantly higher NLS, compared with SBD- [HR=0.37; 95%CI (0.24-0.68); P=.001; Figure].

**Conclusions:** The NAPPED consortium has resulted in the largest cohort yet of genetically defined FIC1-def and BSEP-def patients. These initial results provide insights into the natural course of these diseases and shed light on the relationships between genotype and the effects of medical and surgical treatments.
Observed native liver survival in mild or medium BSEP-def patients who had undergone surgical biliary diversion (dotted line, n=41) or not (solid line, n=135), using a clock-reset approach.

Disclosure of interest: H.J. Verkade is a consultant for Albireo AB, Ausnutria Hyproca, Friesland Campina Dairy Foods, Danone/Nutricia Research. R.J. Thompson is a consultant for Albireo, Shire, Alexion, Arcturus, Retrophin, and GSK. H. Arnell is a consultant for Albireo, Alexion, and Baxter and does not hold stock in any pharmaceutical companies. B. Fischler is a consultant for Albireo and received travel support from AbbVie.

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Alginate encapsulated hepatocytes for treatment of paediatric failure in children: first clinical experience

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Objectives and Study: Hepatocyte Transplantation is a potential therapy for acute liver failure in children and may bridge the child to either native liver recovery or to the availability of a suitable organ for transplantation. Hepatocytes can be cryopreserved and are thus available in the acute setting. Administering hepatocytes to a coagulopathic critically unwell child is challenging. We have devised a minimally invasive method where hepatocytes are encapsulated in alginate, a bioinert material which serves as both structural support and protection from the immune system, and infused into the intraperitoneal cavity. We performed a pilot study to demonstrate the safety and feasibility of the technique and to assess preliminary efficacy.

Method: Hepatocytes were isolated under GMP conditions from donor livers which were otherwise unsuitable for transplantation. Cells were cryopreserved until required, then thawed and encapsulated in 1.5% SLG20-alginate solution using an encapsulator. 2.5 million hepatocytes per ml of alginate were used to form microbeads (HMB) 0.5mm in diameter. Appropriate ethical and regulatory approval were obtained. Children with acute liver failure who met criteria including an INR> 3.5 were recruited following informed consent from their caregivers. Children were otherwise monitored and managed as per standard of care including listing for liver transplantation.

Results: Eight children were treated over a 4-year period. The median age was 15 days. Diagnosis was Neonatal Hemochromatosis in 5, disseminated herpes simplex type 1 infection in 1, adenovirus-associated in 1 and idiopathic in 1. Median INR at admission was 2.3 and total bilirubin 136 umoll/l. Median maximum INR was 5.8. Intraperitoneal transplantation of HMBs was performed between day 3 and 8 of admission while the child was in ICU. Two patients received a second infusion a week after the first. All patients tolerated the infusion well with no complications. Four of 8 patients recovered with their native liver and avoided the need for liver transplantation. Three patients were successfully bridged to liver transplant, in two of these children, the waiting time to liver transplant was > 3 weeks. Care was withdrawn in the remaining child in view of a complex uncorrectable cardiac abnormality and the child subsequently died. Clinical and biochemical improvement was noted in 5 children with an improvement of INR within 24 - 48 hours post infusion. The HMB were electively washed out of the patients' abdominal cavity at time of transplant or laparoscopically between 3 and 6 months after HMB infusion. At the 6-month time point, adhesions were noted but were not causing obstruction. There have been no further complications with a follow up between 2 and 6 years.

Conclusion: Though data are preliminary, HMB encapsulated in alginate and injected intraperitoneally in children with ALF, seems to be safe, feasible and potentially a promising new therapy for acute liver failure in children.

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Development and validation of a new diagnostic scoring system for paediatric autoimmune hepatitis based on the ESPGHAN and NASPGHAN 2009 proposal

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Objectives and Study: Children with autoimmune hepatitis (AIH) often exhibit lower autoantibodies titres than adults. Moreover, autoimmune sclerosing cholangitis and overlap syndrome require exclusion as they can easily be mistaken for AIH. Taking into account these particularities, seven paediatric-specific criteria have been proposed (JPEN. 2009; 49:159). We hypothesized that 2009 criteria can function adequately as a diagnostic tool. Our aim was to develop a prediction model based on them, transform it into a scoring system and study its accuracy.

Method: We selected a cohort of children under study for possible AIH through consecutive sampling retro- and prospectively. AIH diagnosis was based on the 1999 original criteria. Paediatric 2009 criteria were recorded as independent binary variables, except the autoantibodies criterion, which was categorised into three levels. The prevalence of AIH within the cohort was obtained. Study period from 2006 to 2017. Needed sample size was previously calculated. The whole sample was randomly split into two parts: the training and the validation set. All possible models were studied through logistic regression using the training set. The best model according to Akaike information criterion and Nagelkerke's R² was selected. The standardized beta coefficient of each criterion was translated into a whole number (points) maintaining the proportion between them. Total scores were obtained following the points system and the best cut-off was calculated. Subsequently, validity indicators of the new diagnostic scoring system, based on the 2009 criteria, were estimated using the validation set: sensitivity (Se), specificity (Sp), likelihood ratios and predictive values (PV). We also calculated the area under the receiver operating characteristic curve (ROC) for the point system and for the diagnostic classification based on the optimal cut-off.

Results: A total of 212 cases were included. Among them, 100 cases were AIH, demonstrating a prevalence of 47.2%. The non-cases group included a variety of diagnoses like viral hepatitis, toxic hepatitis, Wilson’s disease, acute cryptogenic hepatitis, primary sclerosing cholangitis, or non-alcoholic steatohepatitis. The finally chosen regression equation was that from the model with only 5 criteria: autoantibodies, hypergammaglobulinemia, liver histology, exclusion of viral hepatitis and exclusion of Wilson's disease (R² 0.967 and area under ROC curve 0.994). The table below depicts the beta coefficient for each criterion and the number of points assigned. The selected scoring system admits a maximum of 8 points. Optimal cut-off was fixed at 6 points. The validation set included 70 patients (24 with AIH). In this subsample, Se and Sp was 95.8% and 100% respectively. Positive PV for the found prevalence was 100% and the negative PV was 96.4%. The area under the ROC curve for the scoring system was 97.1% (and 97.9% for the selected cut-off).

Conclusion: Paediatric-specific criteria for the diagnosis of AIH can be used as a scoring system, providing good sensitivity and specificity. Children with a positive result (6 points and over) can be reliably diagnosed of AIH. Although the cholangiogram criterion was not included, considering current knowledge and clinical evidence, imaging of the biliary tract should be performed.
<table>
<thead>
<tr>
<th>Diagnostic criterion</th>
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<tr>
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</tr>
<tr>
<td>Negative autoantibodies</td>
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<tr>
<td>Low-positive autoantibodies*</td>
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<td>19.088</td>
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<tr>
<td>Exclusion of Wilson's disease</td>
<td>18.885</td>
<td>1</td>
</tr>
</tbody>
</table>

*Low-positive autoantibodies: antinuclear antibodies and anti-smooth muscle $\geq 1:20$ and $<1:80$, with anti-LKM1 $\geq 1:10$ and $<1:80$, and both anti-LC1 and anti-SLA/LP negatives. **High-positive autoantibodies: antinuclear antibodies and anti-smooth muscle $\geq 1:80$, or anti-LKM1 $\geq 1:80$, or either anti-LC1 or anti-SLA/LP positive.

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Chronic rejection after paediatric liver transplantation: impact of the vanishing bile duct syndrome on long term graft survival

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Objectives and Study: Chronic rejection (CR) is a relevant complication in the long term follow up after liver transplantation, as a cause of graft dysfunction and eventually of possible graft loss. The diagnosis of CR in paediatric series ranges from 8 to 13%. The aim of this study was to evaluate the prevalence of CR, defined as vanishing bile duct syndrome on histological samples, in a wide population of paediatric patients who underwent liver transplantation across different transplantation periods; to define the progression from “early” chronic rejection (ECR), potentially reversible, to “late” chronic rejection (LCR), theoretically irreversible, and to evaluate the impact of the CR diagnosis on long term graft loss, in comparison with the group of patients who are not affected by CR.

Method: All children who underwent liver transplantation at our Liver Transplant Unit from 1997 to 2013 were considered for retrospective analysis. All patients with CR and at least 3 years of follow up where included. The diagnosis of CR was based on per-cause liver biopsy, performed when transaminases and/or GGT levels were >2 times the normal value, in >2 serial control visits. The Banff Criteria were the gold standard to define the diagnosis of CR, with the “vanishing” of the bile duct as the main parameter. To evaluate the impact of the different transplantation eras, the studied population was divided in 2 subgroups: 1997-2005 and 2006-2013.

Results: The 2 subgroups related to different eras didn't show any statistically significant difference in the total prevalence of CR, despite different treatment and general management. In the whole study period (1997-2013) 83 grafts (81 patients)/528 (467 patients) (15.7%) were diagnosed with CR (ECR or LCR); the mean time at the diagnosis was 3.3 (±3.5) years after liver transplantation. At the first diagnosis, 49/83 (59%) of the grafts presented as ECR, 28/83 (34%) as LCR; in 6 grafts the diagnosis was not clearly defined. Progression from ECR to LCR was observed in 20/49 (41%) grafts at 3 years, 24/49 (49%) at 5 years, 30/49 (61%) at 10 years of follow up. These results were pooled with those with a first diagnosis of LCR. Among all grafts with LCR, the graft loss after 3, 5 and 10 years after transplantation occurred in 6.4%, 7.9% and 11.1%, whereas patient mortality was 0, 0 and 1.6% respectively. The majority of patients with CR had a good quality of life and show a preservation in liver synthetic function, despite abnormalities in transaminases and cholestasis tests. The comparison between the graft survival of CR and non-CR patients from the same transplantation era showed no difference in the 2 groups (Figure 1).
Conclusion: The prevalence and progression of CR in a population of liver transplanted children is stable across different eras, with different management and treatment strategies. Despite the progression of ECR to LCR in a large proportion of cases, after a 10 years' follow up the diagnosis of CR doesn't show a significant impact on patient and graft survival, as compared to patients without CR.

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The thrombogenic risk induced by intraportal infusion of Adult Derived Human Liver Stem/Mesenchymal Cells in Wistar rats can be controlled with a combination of anticoagulant drugs, heparin and bivalirudin

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Objectives and Study: Mesenchymal Stem cell (MSC) transplantation is a fast emerging therapy for regenerative medicine. However MSCs express a procoagulant activity (PCA) inducing a thrombogenic risk in recipient patients. This thrombogenic risk is due to activation of the coagulation cascade, triggered by Tissue Factor (TF) on MSCs, resulting in fibrin production and platelet consumption. In vitro the PCA of Adult Derived Human Liver Stem/Mesenchymal Cells (ADHLSCs) can be controlled by an anticoagulant cocktail, combining an antithrombin activator (Heparin) and a thrombin inhibitor (Bivalirudin). The aim was to study in vivo, the effect of an anticoagulant cocktail on thrombogenic risk induced by intraportal ADHLSCs. First we wanted to characterize the thrombogenic events induced by ADHLSCs infusion. Then we wanted to study the effect of the anticoagulant cocktail on these events. Finally the effect of cell dosage on the thrombogenic risk was studied.

Method: Wistar rats (n=3 per group) were infused with 3 different cell dosages (50, 12.5 and 5 million ADHLSCs/kg), with or without anticoagulant therapy through an intraportal catheter. Control group was infused with PBS. Blood samples were collected before and 1 hour after cell infusion. Rats were sacrificed and liver tissue was collected 1 hour after cell infusion. Serial slides were performed to analyse the localisation of AHDLSCs and fibrin.

Results: ADHLSCs intraportal infusion induced after 1 hour a significant decrease (p &LT; 0.05) in platelet count with production of fibrin around the infused cells localized in PVs. No platelet consumption or fibrin production was observed in the control group. In the anticoagulated group, platelets also decreased significantly (p &LT; 0.05) but fibrin production was significantly (p &LT; 0.001) reduced, from 86.6% ± 6.4 to 26.4% ± 13.8. When different cell dosages were infused, we observed a correlation between the number of infused cells and the number of cells in the liver. The number of cells in liver tissue (cells/mm²) and the number of PVs containing cells (PVs containing cells/total PV) were significantly (p &LT; 0.01) lower when lower cell dosages were used, compared to the higher cell dosage group. Consumption of platelets was also correlated to cell dosage. No decrease in platelets was observed when 5x10⁶ cells/kg were infused without anticoagulation, and when 12.5x10⁶ cells/kg were infused with anticoagulation. Platelets tended to decrease less in the high cell dose group, 50x10⁶ cells/kg when anticoagulation was administered. No significant difference has been observed in the production of fibrin in PVs between the different cell dosages. In all conditions, hemoglobin did not decrease significantly, meaning that blood sampling did not interfere with our results.

Conclusion: Intraportal infusion of ADHLSCs activated the coagulation cascade resulting in fibrin formation and platelet consumption 1 hour after cell infusion. The use of a combination of anticoagulant drugs, heparin and bivalirudin, could prevent the formation of fibrin, but a significant decrease in platelets was still observed. However this decrease tends to be less and can even be controlled when lower cell dosages are used. The production of fibrin and thus the activation of the coagulation cascade was not dependent of cell dosage.

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Next generation sequencing in the diagnostic approach to neonatal/infantile cholestasis

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Objectives and Study: Next generation sequencing (NGS) offers the opportunity to significantly improve the diagnostic yield in paediatric hepatology. Aim of this prospective study was to evaluate a diagnostic protocol for neonatal and infantile cholestasis (NIC) in which a NGS targeted liver panel (TLP), or a clinical exome sequencing (CES) in selected cases, was used early after the exclusion of the surgical causes.

Method: We included patients with cholestasis (hyperbilirubinemia with direct component >20% of the total) persisting ≥6 weeks with onset ≤ 1 year of age referred to our tertiary centre between January 2012 and June 2017. Preterm infants or those receiving ≥ 2 weeks of parenteral nutrition were excluded. The TLP allows sequencing of 27 genes of 25 genetic causes of NIC. The CES used in this study is the TruSight One (Illumina Inc, San Diego, US), that includes 4813 disease genes.

Results: We enrolled 122 children (65 female), with a median age of 5.5 months (1 month-2.5 years) at first visit. The ethnicity was Caucasian in 106 (86.7%), African in 12 (10%) and Asian in 4 (3.3%). Consanguinity was present in 5 (4.1%). In 4 (3.3%) a history of liver disease in the first-degree relatives was documented. Major and minor dysmorphisms or malformations were present in 26 (21.3%). Laboratory tests showed (median, range): ALT 140 IU/L (36-925), total bilirubin 9 mg/dL (2.3-54), GGT 178 IU/L (14-2200). Coagulopathy (PT > 1.3) was present in 33 (27%).

Ninety-six (78.7%) patients had hypo-acholic stools: these children were rapidly evaluated to rule out biliary atresia (BA), which was the final diagnosis in 72/96 of them. Neonatal sclerosing cholangitis, biliary malformation and autoimmune sclerosing cholangitis were diagnosed in 1 each. The remaining 21/96 had NGS analysis: 6 patients in whom intraoperative cholangiography did not confirm the suspect of BA; 3 who did not undergo surgery for late referral; 8 in whom liver biopsy showed giant cell transformation; 2 patients with clinically evident Alagille syndrome (AGS); 2 with low serum alpha1-antitrypsin (A1AT). NGS was the first-step analysis in 26 children with normal stools (16 with raised GGT and 10 with normal GGT) (Figure).

Overall, 47 children had NGS (TLP in 45), and a diagnosis was achieved in 26 (detection rate: 55%). CES was preferred as first choice in 2 patients with complex phenotype. The final diagnosis was AGS in 11 (9%); PFIC2 in 6 (4.9%); A1AT deficiency in 3 (2.5%); PFIC 3 in 2 (1.6%); PFIC1, Niemann-Pick type B, Gaucher disease in 1 child each. Only 18/122 (14.8%) patients had an indeterminate aetiology. The median diagnostic turnaround time was 43 (38-55) days.

Conclusion: Focused genetic testing through NGS, used in appropriate clinical protocols, is a smart diagnostic tool, capable of identifying most genetic disorders causing NIC with a high detection rate. It also allows a non-invasive diagnosis in children presenting without hypo-acholic stools, with reasonable turnaround time.
[Results of the NGS-centred protocol of neonatal/infantile cholestasis.]

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MRI as a biomarker for Wilson's disease in children: Early observations from a larger trial into pediatric liver disease

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Introduction: Wilson disease (WD) is a rare autosomal recessive inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, and other tissues. Diagnosis may be difficult and often involves a combination of blood tests, urine tests, and a liver biopsy, as well as genetic testing. Since severe liver damage can occur before there are any other signs of the disease. The ability to distinguish WD patients who present with liver symptoms from those with other liver-related disease would be beneficial to the early detection and thus treatment of the disease.

Liver biopsy is the gold standard for evaluating liver pathology, but it is risky, costly and lacks validation in pediatric populations. MRI-derived iron corrected T1 (cT1) is a promising technique that has demonstrated utility in stratifying patients with liver disease in adults. This study (NCT03198104) is aimed at evaluating this MRI based technique in a large sample of children with a variety of liver diseases.

Methods: We investigated 54 paediatric patients (30 female; mean age 13.4 [range 6-17 yrs.], 5 with WD (mean age 9.1 [7-10]) and 49 others with various liver diseases (AIH (n=38), PSC (n=6), other (n=5)). All participants underwent multi-parametric MRI with the LiverMultiScan™ protocol (acquisition time < 10 mins) from which cT1 maps, and also a measure of liver fat (PDFF) were derived. cT1 has been shown to correlate with fibro-inflammatory disease and predict liver-related outcomes in adults. Comparisons between groups for cT1 and % liver fat were performed using two-sided Kolmogorov-Smirnov (KS) tests, and cut-offs that could separate WD from other liver diseases explored.

Results: WD group had significantly higher cT1 (P < .01) and PDFF (P < .001) compared to the other liver diseases (figure 1). In an enrichment analysis designed to classify the groups from each other, a cut-off of liver fat ≥10% and cT1 ≥ 750ms, successfully separated the WD from the other patients.

Conclusions: Early results indicate that LiverMultiScan™ may be a promising, fast and non-invasive technique for stratifying children with WD from other types of liver disease.
References:

This study was funded by The National Centre for Research and Development (Poland) and InnovateUK under EUREKA/Eurostars project E!10124 “Kids4LIFe - Assessing Kids for Liver Inflammation and Fibrosis using noninvasive MRI.”

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Mutations in MYO5B in early onset cholestasis

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Objectives and Study: Mutations in myosin 5B (MYO5B) are known to be associated with microvillous inclusion disease (MVID) and intestinal failure associated liver disease. A small number of children have been recently described with mutations in MYO5B, who developed cholestasis with no typical symptomatology of MVID. We report our case series.

Methods: Patients with cholestasis and pathogenic mutations in MYO5B, found by Next Generation Sequencing (NGS), and minimal gastrointestinal disease were studied. Clinical, laboratory and histological data were collected.

Results: Five patients (2 M) were identified. Median age at presentation was 19 months (range 8-92). Presenting features were jaundice (2), pale stools (2), dark urine (1), failure to thrive (2), pruritus (4). Patient 5 had intractable diarrhoea up until age of 3 yrs; since then she has been on full enteral diet with no intestinal symptoms. Median values (range) for serum total bilirubin (SBR) were 55 µmol/L (2-500), aspartate aminotransferase (AST) 73 I U/L (32-114), y-glutamyltransferase (GGT) 7I U/L (7-10), INR 0.86 (0.8-0.99), albumin 41 g/L (35-47), serum bile acids (BA) 134 µmol/L (18-274). MYO5B mutations are listed in table. Patients 1 and 5 underwent external biliary diversion at 3 yrs and 2 yrs and nasobiliary drainage at 15 yrs, respectively. Patient 2 had internal biliary diversion at 2 yrs with minimal improvement, which then was externalised at 4yrs 10mths with good effect. Pruritus recurred in patients 1 and 5 after 2, 3 and 6 months, respectively. Patient 5 had single pass albumin dialysis with temporary symptom improvement. Median follow up was 3 years (2-9). At most recent follow up they all reported pruritus while on antipruritics, loose stools (2/5) on full enteral feeds with median SBR 3I µmol/L (2-290), AST 35 IU/L (26-39), GGT 10 IU/L (8-31), INR 1 (0.94-1.2), serum BA 72 µmol/L (3-316) and albumin 41 g/L (38-42). Patient 1 is currently being considered for liver transplantation (LT). Liver biopsies were undertaken on all patients (at ages 1, 2, 7 and 10 years). Fibrosis varied from nil (1) to mild portal and perivenular fibrosis (3). Cholangiopathic features were not seen. In all patients, there was canalicular cholestasis in perivenular areas, biliary rosette formation and minimal lobular disarray, with additional focal giant cell changes and mild lobular activity in patients 1 and 2. All patients demonstrated reduced canalicular GGT and CD10 expression in centrilobular areas and preserved canalicular BSEP expression.

Conclusion: We identified five patients, with mutations in MYO5B, and early onset cholestasis and severe pruritus in 3, non-responsive to biliary diversion. Progressive liver disease was evident on 3 of 5 biopsies without typical MVID intestinal disease. The severity of cholestasis was enough for LT to be recommended in one.
<table>
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<th>Patient</th>
<th>Zygosity</th>
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<th>Amino acid change</th>
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*Mutations in MYO5B identified by NGS and confirmed*
Capturing T-cell receptors. A potential new modality for targeting hepatic tumours and Post-Transplantation Lymphoproliferative Disease (PTLD)

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Background: Malignant cells express cell surface proteins. These are believed to be targets of the immune system. When this process goes wrong, a tumour forms. This therefore is a potential target for cancer specific immunomodulatory treatment.

Aim: (1) Identify tumour-specific MHC-class-I phosphopeptide antigens on lymphoblastoid cells (in vitro model for PTLD) and hepatic tumours. (2) T-cells are immune cells difficult to maintain in long-term culture. We proposed using induced pluripotent stem cell (iPSc) technology to immortalise and exponentially expand T-cells. (3) By co-culturing with OP9 DL1 cells, can iPSc be differentiated back into a stable and functional T-cell, thus generating a non-patient-specific, but tumour-specific product.

Patients/methods: Patients were identified with hepatic malignancy. Cells were isolated and tumour-specific phosphopeptide antigens were identified.

Results: A number of novel phosphopeptide antigens were identified. This information has been used to identify potential T-cell targets. We have developed phosphopeptide specific T-cell lines as a result. By generation of iPSc from these, we have established a method for expanding specific T-cell’s exponentially in vitro. These iPSc are more stable than the T-cell lines they were derived from. Using OP9DL1 cells we have established a modality for differentiating stable iPSc back into a T-cell which potentially has the same specificity as the parent line. This therefore provides potential for the generation of a tumour specific T-cell product.

Conclusions: Identifying modalities for expanding cells with a specific TCR repertoire targeting tumour-specific phosphopeptide antigens has the potential to be developed as an immunomodulatory therapy in patients with hepatic tumours/PTLD.

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Transient neonatal cholestasis of unknown cause is associated with heterozygosity for pathogenic mutations in SERPINA1 or other genes involved in cholestasis

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Objectives and Study: Transient neonatal cholestasis (TNC) is a frequently unresolved clinical entity, characterized by neonatal cholestasis that spontaneously resolves, usually within months. TNC may be related to perinatal infections, prematurity, perinatal asphyxia, and extended parenteral nutrition. However, a subcategory remains in which no cause is identified. Heterozygosity for pathogenic gene mutations implied in cholestasis, such as alpha-1 antitrypsin (A1AT) Z-genotype, has been associated with non-alcoholic steatohepatitis or other forms of liver disease upon specific challenges later in life. We hypothesized that such a carrier state is also associated with TNC of unknown cause. We tested whether carrier state for pathogenic mutations in SERPINA1 (the gene for A1AT) or in the canalicular transporters ATP8B1 (progressive familial intrahepatic cholestasis type 1; PFIC1), ABCB11 (PFIC2), ABCB4 (PFIC3) occurred more frequently in patients with TNC of unknown cause.

Method: We retrospectively included patients with TNC of unknown origin. TNC was defined as cholestasis occurring before the age of one month and normalization before the age of 6 months, with cholestasis defined as serum direct bilirubin above 40 µM. TNC was considered of unknown origin in case of absence of a (likely) etiological diagnosis detected by classic diagnostic work-up for neonatal cholestasis. This included evaluation of obstructive biliary pathology, infectious causes, metabolic causes (i.a. ZZ-A1AT deficiency), endocrine causes, signs of Alagille syndrome, and bile acid synthesis disorders. To limit confounding factors, we excluded patients in case of prematurity (< 36 wk gestational age; GA), perinatal asphyxia, sepsis, and parenteral nutrition. Genetic evaluation was done by next-generation exome sequencing. We compared occurrence of pathogenic mutations to the expected occurrence of heterozygosity in the general population, based on previously reported frequencies in the Genetics Home Reference (National Institutes of Health, USA) and Oxford Desk Reference on Clinical Genetics and Genomics. Values are in medians with total range.

Results: We included 10 patients with TNC of unknown cause; 6 M/ 4 F. GA age was 39+1 weeks (36+5 - 40+1) and birth weight 2945 grams (1740 - 3846). Peak level of direct bilirubin was 85 µM (60-154) and the age at which cholestasis completely resolved was 106 days (62-151). Four out of 10 patients (40%) were heterozygous for a pathogenic mutation in SERPINA1, versus an expected 10/100 (10%, P=0.023). In 2 of the 10 patients heterozygosity for a pathogenic mutation in ATP8B1, ABCB11, or ABCB4 was found versus an expected heterozygosity rate of 1/100 (P=0.021). One patient was heterozygous for both ABCB11 and SERPINA1. Combined, 5/10 patients were heterozygous for a pathogenic mutation in genes related to either PFIC 1,2,3 or A1AT deficiency, versus an expected 11/100 (P=0.006).

Conclusion: Our data indicate that carrier state for A1AT deficiency or for pathogenic mutations in genes responsible for PFIC 1, 2 or 3 is strongly associated with transient neonatal cholestasis of unknown cause. We hypothesize that the transient “immature” bile acid composition, specific for the neonatal state, elicits the TNC and that the cholestasis resolves upon maturation of the bile physiology.


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BMP-2 restoration rescues liver fibrosis injuries by attenuating TGF-β1 signaling

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Objectives and Study: Transforming growth factor-β (TGF-β) plays a central role in hepatic fibrogenesis. This study investigated the function and mechanism of bone morphogenetic protein-2 (BMP-2) in regulation of hepatic fibrogenesis.

Method: BMP-2 expression in fibrotic liver was measured in human tissue microarray and mouse models of liver fibrosis induced by bile duct ligation (BDL) surgery or carbon tetrachloride (CCl₄) administration. Adenovirus-mediated BMP-2 gene delivery was used to test the prophylactic effect on liver fibrosis. Primary hepatic stellate cells (HSC) and a cell line, HSC-T6 cells, were used to study the interplay between BMP-2 and TGF-β1

Results: Hepatic BMP-2 expression was significantly decreased in either human fibrotic tissues or mice fibrosis models, with a negative correlation with hepatic TGF-β1 contents. BMP-2 gene delivery alleviated the elevations of serum hepatic enzymes, HSC activation markers, and liver fibrosis in both models. Mechanistically, exogenous TGF-β1 dose-dependently reduced BMP-2 expression, whereas BMP-2 significantly suppressed expression of TGF-β and its cognate type I and II receptor peptides, as well as the induced Smad3 phosphorylation levels in primary mouse HSCs. Aside from its suppressive effects on cell proliferation and migration, BMP-2 treatment prominently attenuated the TGF-β1-stimulated α-smooth muscle actin and fibronectin expression, and reversed the TGF-β1-modulated epithelial-to-mesenchymal transition marker expression in mouse HSCs.

Conclusion: The mutual regulation between BMP-2 and TGF-β1 signaling axes may constitute the anti-fibrogenic mechanism of BMP-2 in the pathogenesis of liver fibrosis. BMP-2 may potentially serve as a novel therapeutic target for treatment of liver fibrosis.

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MicroRNA-29a mitigation of endoplasmic reticulum and autophagy aberrance counteracts in obstructive jaundice-induced fibrosis in mice

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Objectives and Study: Hepatic fibrosis was caused by a number of signaling pathways that damage liver integrity. We have previously shown that microRNA-29a (miR-29a) protects against liver fibrosis. Aberrant endoplasmic reticulum (ER) and autophagy function reportedly exaggerate hepatic disorders. The aim of this study was to characterize the biological influence of miR-29a on ER function in injured livers with bile duct ligation (BDL).

Method: We performed BDL on miR-29a transgenic mice (miR-29aTg) and wild-type mice to induce cholestatic liver injury. Rat T6 cells were transfected with miR-29a mimic and tunicamycin.

Results: Compared to the wild-type mice, the BDL deterioration of liver function in terms of total bilirubin, alanine transaminase, and aspartate transaminase activity in the miR-29aTg mice was significantly reduced. Affected livers in the miR-29aTg mice demonstrated a slight fibrotic matrix formation. miR-29a overexpression reduced the BDL disturbance of the expressions of inositol-requiring kinase 1alpha, double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase, Spliced-X-box binding protein 1 (sXBP1), CCAAT/enhancer-binding protein homologous protein (CHOP), ULK, LC3BII, p62, and cleaved caspase-8, 9 and 3. In vitro, T6 cells exposed to tunicamycin by increasing abundances of CHOP, sXBP1, cleaved caspase-3 and LC3BII were diminished in the cell cultures transfected with the miR-29a mimic. On the other hand, we observed that miR-29a signaling protected liver tissues from BDL-mediated metabolic dysfunction and excessive fibrosis histopathology.

Conclusion: This study provides new molecular insight into the miR-29a stabilization of ER integrity that slows the progression of cholestatic liver deterioration.

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Prospective evaluation of sclerosing cholangitis in children with autoimmune liver disease

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Objectives and Study: Overlap of autoimmune hepatitis (AIH) and primary sclerosing cholangitis is labelled as autoimmune sclerosing cholangitis (ASC) in children. The only study in children has shown a high prevalence of ASC by using ERCP. Aims of our study were to find the prevalence of ASC by using Magnetic resonance cholangiography (MRC) in AIH and in non-AIH cirrhosis, and to compare clinical presentation and outcome of AIH and ASC.

Method: Prospectively we did MRC in 38 children with AIH (cases) and 19 disease controls with non-autoimmune, non-cholestatic causes of chronic liver disease. (Wilson disease). Biliary strictures with proximal dilatation on MRC was taken as definitive changes of ASC. Details of clinical, laboratory parameters, liver histopathology and treatment outcome were recorded. One child was excluded due to poor MRC imaging.

Results: The median age of cases was 11.5 (3-18) years and 22 (55%) were girls. Majority (74%) were diagnosed as type 1 AIH. MRC was done in 11 children (29%) at the time of diagnosis and in 21 (71%) after a median follow-up of 2.5 (0.3-10) years. Abnormal MRC changes were seen in 14/38 (37%) and 8/19 (42%) in children with AIH and controls. However, definite changes of ASC were present in 4 (10.5%) children in cases and none in controls. None of the clinical, laboratory, histological parameters and treatment response were significantly different between ASC and AIH groups.

Conclusion: The prevalence of ASC in children with AIH was just 10.5%. Clinical, biochemical, histological features and treatment response were similar in both ASC and AIH. We suggest MRC in select group of children instead of all children with AIH.

<table>
<thead>
<tr>
<th>MRC</th>
<th>AIH n=38 (%)</th>
<th>Controls n=19 (%)</th>
<th>Controls n=19 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver parenchymal heterogeneity</td>
<td>24 (63)</td>
<td>17 (90)</td>
<td>0.06</td>
</tr>
<tr>
<td>Surface irregularities</td>
<td>22 (58)</td>
<td>14 (74)</td>
<td>0.38</td>
</tr>
<tr>
<td>Confluent fibrosis</td>
<td>5 (13)</td>
<td>3 (16)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intrahepatic ductal irregularity</td>
<td>4 (10)</td>
<td>2 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intrahepatic focal narrowing (single or multiple)</td>
<td>7 (18)</td>
<td>4 (21)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intrahepatic multiple stricture with dilatation (Beaded appearance)</td>
<td>2 (5)</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Extrahepatic focal narrowing (single or multiple)</td>
<td>5 (13)</td>
<td>5 (26)</td>
<td>0.28</td>
</tr>
<tr>
<td>Extrahepatic single and multiple stricture with dilatation</td>
<td>2 (1 each:5)</td>
<td>0</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Comparison of MR cholangiogram in AIH and controls

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Objectives and Study: Diagnostic criteria for Pediatric autoimmune liver disease (AILD, encompassing both autoimmune hepatitis/AIH and autoimmune sclerosing cholangitis/ASC), were extrapolated from criteria established primarily in adult population. Limited pediatric studies are available regarding their validity in Asian population, and new proposed ESPGHAN score (year 2017) also remains untested. We thus aimed to validate these criteria in the local cohort.

Method: A review of all pediatric AILD cases presenting over a 6 year period was done. Diagnostic criteria for AIH included classical histological criteria, while ASC was diagnosed based on features of AIH along with either abnormal cholangiographic study (multiple strictures and/or dilatations of biliary tree) or histological evidence of primary bile ductal injury (fibro-obliterative cholangitis etc). To validate different diagnostic scores (Original pre-treatment (year 1999) score/Simplified (year 2008) score/New proposed ESPGHAN (year 2017) score), apart from the study cohort, we included consecutive pediatric non-AILD liver disease subjects as a control group (in 1:1 ratio). These scores were then compared and agreement analysis was done.

Results: Final study groups included 85 subjects in AILD group (70 AIH and 15 ASC patients) and 85 consecutive subjects in non-AILD group.

When analysed for diagnosis of AILD in the total cohort, as shown in table 1, all three scores had area under ROC (AUROC) curves exceeding 0.9 suggestive of excellent discrimination of AILD (Original score: 0.970, 95 % C.I 0.950 to 0.990, Simplified score: 0.974, 95 % C.I 0.956 to 0.993; and new ESPGHAN score: 0.959, 95 % C.I 0.931 to 0.986). Similar results were found on subgroup analysis also: for discrimination of only total AIH subjects (AUROC 0.979, 0.981 and 0.976 respectively); for discrimination of only seropositive AIH subjects (AUROC 0.984, 0.986 and 0.981 respectively); for discrimination of only seronegative AIH subjects (AUROC 0.963, 0.962 and 0.959 respectively); and for discrimination of only ASC subjects (AUROC 0.927, 0.945 and 0.879 respectively).

When the AUROC curves were compared between the three scores, there was no statistical difference between them (Original versus simplified score: p 0.323; Original versus new ESPGHAN score: p 0.441; and Simplified versus new ESPGHAN score: p 0.821). Thus, the prediction value for AILD was similar for all the three scores. Similar results were obtained on subgroup analysis also as done earlier.

Agreement between different scores was analysed by using intraclass correlation coefficient (ICC). The ICC between new ESPGHAN score and simplified score was 0.81 (95 % C.I 0.72 to 0.87) suggestive of good reliability. Similar analysis between new ESPGHAN score and original score (ICC 0.54, 95 % C.I -0.04 to 0.76), and between simplified score and original score (ICC 0.40, 95 % C.I -0.11 to 0.66) was suggestive of moderate and poor reliability respectively.

Conclusion: There is no difference in the predictive value of the three scores for pediatric AILD, with all having excellent efficacy for the same. There is good agreement between the simplified and new ESPGHAN score. Larger multicentre studies across all populations are needed to provide further evidence.

Table 1: Comparison of the scores for total cohort
<table>
<thead>
<tr>
<th>Score</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Correctly Classified</th>
<th>AUROC (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original score (Cut off &gt; 10)</td>
<td>96.5 %</td>
<td>81.2 %</td>
<td>83.7 %</td>
<td>95.8 %</td>
<td>88.8 %</td>
<td>0.970 (0.950 - 0.990)</td>
</tr>
<tr>
<td>Original score (Cut off &gt; 15)</td>
<td>64.7 %</td>
<td>98.8 %</td>
<td>98.2 %</td>
<td>73.7 %</td>
<td>81.8 %</td>
<td>0.974 (0.956 - 0.993)</td>
</tr>
<tr>
<td>Simplified score (Cut off &gt; 6 )</td>
<td>90.6 %</td>
<td>94.1 %</td>
<td>93.9 %</td>
<td>90.9 %</td>
<td>92.4 %</td>
<td>0.974 (0.956 - 0.993)</td>
</tr>
<tr>
<td>Simplified score (Cut off &gt; 7)</td>
<td>57.6 %</td>
<td>100 %</td>
<td>100 %</td>
<td>70.2 %</td>
<td>78.8 %</td>
<td>0.959 (0.931 - 0.986)</td>
</tr>
<tr>
<td>New proposed score (Cut off &gt; 7)</td>
<td>85.9 %</td>
<td>94.1 %</td>
<td>93.6 %</td>
<td>87 %</td>
<td>90 %</td>
<td>0.959 (0.931 - 0.986)</td>
</tr>
<tr>
<td>New proposed score (Cut off &gt; 8)</td>
<td>69.4 %</td>
<td>96.5 %</td>
<td>95.2 %</td>
<td>75.9 %</td>
<td>82.9 %</td>
<td>0.959 (0.931 - 0.986)</td>
</tr>
</tbody>
</table>

*[Table 1: Comparison of the three diagnostic scores]*

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Sustained biochemical response to oral antibiotics in pediatric PSC and ASC is correlated to changes in gut microbiota and serum bile acids during therapy

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Objectives and Study: Concomitant presence of autoimmune hepatitis and primary sclerosing cholangitis (PSC) is labelled as autoimmune sclerosing cholangitis (ASC) in children. Based upon the possible implication of microbiota and microbial metabolites, such as bile acids (BAs), in the pathogenesis of PSC, oral antibiotics are increasingly being used as a novel therapeutic approach and shown to have benefit in PSC but their role in pediatric ASC is not well evaluated. We prospectively analysed the gut microflora and serum BAs pool before and after antibiotic therapy in children with ASC or PSC alone, and evaluated whether changes in gut microflora and/or BAs correlated with response to treatment.

Method: Patients diagnosed with ASC or PSC on basis of biochemical, liver biopsy and radiology findings were included. They prospectively received metronidazole (MTZ) for 14 days as induction or rescue therapy. MTZ were administrated in addition to the standard treatment of UDCA for PSC patients and azathioprine, and UDCA and/or steroids for ASC patients. Stool and serum samples were collected before and after MTZ therapy. DNA isolation, amplification and Illumina sequencing to profile the microbiota composition were performed using the bacterial 16s rRNA while serum BAs were assessed by ultraperformance liquid chromatography coupled to mass spectrometry. The beta-diversity measured the dissimilarity between each paired stool samples. The outcome parameters to assess the efficacy of antibiotics were reduction liver enzymes and subsequently achievement of sustained biochemical remission.

Results: Seven children (4 ASC, 3 PSC) were included, of which 5 have a concomitant ulcerative colitis (UC). All patients showed a significant decrease in their AST (-55%, p<0.025), ALT (-56%, p<0.025) and GGT (-41%, p<0.025) under MTZ. Three children relapsed after stopping MTZ while the four others children showed a sustained biochemical remission (liver enzymes below 1.5 times upper limit of normal) after a median follow-up of 375 days. Among these four patients, three exhibited a wide different microbial composition before and after MTZ as expressed by the beta-diversity variation. They also expanded their total serum BAs size (from 1542.96 to 2620.99 pmol/100µl, +69.87%), primarily due to the large increment of UDCA and its glycine- and taurine-conjugates which finally represented more than half of the total serum BAs. On the contrary, the microbiota of patients who relapsed remained unchanged pre- and post-MTZ and total BAs pool decreased.

Conclusion: Our study suggests that oral antibiotic could be an effective treatment of ASC and PSC, especially those with a concomitant UC, and that intestinal microflora and BAs play a major role in these diseases as sustained biochemical remission is associated with wide changes in gut microbiota communities and BAs profile after taking antibiotics.

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HEPATOLOGY - General Hepatology

H-O-030

The role of 2-Dimensional Ultrasound Shear Wave Elastography in neonatal/infantile cholestatic jaundice

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Objectives and Study: Prompt differentiation of biliary atresia from other neonatal/infantile liver diseases is necessary for a favorable outcome. Conventional ultrasound is usually the initial imaging modality for infantile cholestatic jaundice. In recent years ultrasound elastography has been developed for assessing liver stiffness and the newest one is the two-dimensional real-time shear wave elastography (2D-SWE). Our purpose of this study was to evaluate the role of 2D-SWE in differentiating biliary atresia from other causes of neonatal/infantile cholestatic jaundice.

Method: The ethics committee of our hospital approved this prospective study. Forty healthy neonates and infants were examined with 2D-SWE as the control group. Twenty-six children younger than 1 year with cholestatic jaundice were examined with 2D-SWE. Conventional ultrasound and doppler imaging of the liver were performed in all study groups. Twelve children underwent liver biopsy. Children with cholestatic jaundice were divided into 2 groups: biliary atresia, mean age 37.7 days (n=10) and non-biliary atresia, mean age 103.37 days (n=16) (other causes of cholestatic jaundice). Mean elasticity values of liver were compared between the groups and they were correlated with findings of ultrasound.

Results: Mean liver elasticity value for the control group was 4.68 ± 0.64, for the biliary atresia group was 14.21 kPa ± 6.87 and for the non-biliary atresia group was 7.35 kPa ± 2.84 (P<LT; 0.05). The two groups with cholestatic jaundice had different reference range of values (6.21 to 49.73kPa for biliary atresia group and 4.59 to 13.26 kPa for non-biliary atresia). In biliary atresia group 2D-SWE revealed higher values in all patients, even in two neonates in the ninth and twentieth day of life, compared to the control group. In the non-biliary atresia group five children had 2D-SWE values similar to healthy children’s and in eight children the values were slightly higher. In three children, all infants > 3 months of age, with non-biliary atresia, 2D-SWE values were significantly higher compared to the control group, but the sonographic findings of the liver in combination with the biochemical profile and the clinical findings allowed follow up. After one-month 2D-SWE values followed the improvement of clinical and biochemical findings of these three infants. Sonographic findings for biliary atresia, both triangular cord sign and abnormal gallbladder were revealed only in four children of this group. Abnormal gallbladder as the only sonographic finding or only triangular cord sign was imaged in the six children with biliary atresia and in these cases the abnormally increased values of 2D-SWE persuaded the referral pediatric gastroenterologist to proceed to immediate biopsy for these neonates. In all children with histologically proven liver fibrosis, 2D-SWE values of liver elasticity were abnormally increased, even in low grades of fibrosis.

Conclusion: 2D-SWE values of liver elasticity are abnormally increased even in very young neonates with biliary atresia and this helps to prompt differentiation from other neonatal/infantile liver disease.

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Anticholestatic drugs as potential treatment for neonatal hyperbilirubinemia

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Objectives and Study: Unconjugated hyperbilirubinemia is transiently present in most neonates and permanently in patients with Crigler-Najjar disease. Severe unconjugated hyperbilirubinemia can induce kernicterus, leading to permanent neurological damage or even death. Phototherapy is the standard treatment, but has not been able to prevent its occurrence, nor eliminate the need for plasma exchange transfusions. We investigated whether ursodeoxycholic acid (UDCA), a secondary bile acid, and obeticholic acid (OCA), a semi-synthetic Farnesoid-X-receptor (FXR) agonist, both anticholestatic drugs, could be beneficial to treat unconjugated hyperbilirubinemia in animal models.

Methods: UDCA was tested in 2 models of neonatal unconjugated hyperbilirubinemia; 1) neonatal Gunn rats, which are completely deficient in the bilirubin conjugation enzyme UGT1A1, and 2) neonatal humanized UGT1A (hUGT1*1) mice. Gunn rats received 250 mg/kg/day UDCA for 7 days and hUGT1*1 pups for 5 days, via oral gavage. OCA (50 mg/kg/day) was administered to hUGT1*1 pups for 5 days.

Results: UDCA significantly decreased total serum bilirubin (TSB) levels by 26% in Gunn rats and by 82% in hUGT1*1 pups. In hUGT1*1 pups, UDCA significantly induced intestinal hUGT1A1 expression, indicating that UDCA can reduce TSB via conjugation-independent (Gunn rats) and -dependent mechanisms (hUGT1A1). UDCA only induced intestinal hUGT1A1, indicating that intestinal conjugation could play a valuable role in bilirubin metabolism.

UDCA did not decrease brain bilirubin in Gunn rats, in contrast to a 77% decrease in hUGT1*1 mice. Similarly, OCA decreased TSB by 62% and brain bilirubin by 69% in hUGT1*1 pups. OCA also induced intestinal hUGT1A1, indicating that the hUGT1A1 increase could be FXR-mediated.

Conclusion: UDCA and OCA can decrease serum and brain bilirubin levels in 2 models of neonatal hyperbilirubinemia via both conjugation-dependent and -independent mechanisms. The data suggest that combining these two mechanisms can effectively decrease brain bilirubin. We postulate that these anticholestatic drugs could serve as novel treatment strategies for unconjugated hyperbilirubinemia.


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Subclinical biliary strictures revealed by mild ductular proliferation in grafts of paediatric liver transplant recipients

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**Objectives and Study:** The reported incidence of biliary complications following paediatric liver transplantation (LT) varies from 5 to 30%. This might be due to different surgical techniques adopted across pediatric LT centres, but may also reflect a different diagnostic approach to subclinical cholestatic hints. So far no useful noninvasive means have been shown to reliably detect a subtle biliary stricture, that may represent a non-immunological culprit to long-term graft dysfunction. In fact, biliary cirrhosis related to unrevealed strictures remains a cause of late graft loss. In our centre, any degree of biliary features detected on liver biopsy leads to perform a percutaneous transhepatic cholangiography (PTC), that is considered the gold standard for identifying and treating biliary stenosis. We aimed to evaluate the role of liver biopsy to predict biliary strictures and distinguish it from other complications in grafts of paediatric LT recipients.

**Methods:** We retrospectively reviewed the data obtained from prospectively managed pediatric LT recipients operated from 2012 and 2015, who had a liver biopsy due to graft dysfunction during their follow up (ALT or GGT greater than 1.5 ULN). PTC was performed in all patients presenting any degree of ductular proliferation on cytokeratin-7 stained histology samples, in the absence of other features responsible for biochemically detected graft dysfunction. The medical records, laboratory reports and imaging reports led to a dataset that was focused on children who had a PTC upon histology indication. Patients with intrahepatic bile ducts diameter >4 mm on ultrasound (USS) were excluded.

**Results:** Out of 202 per-cause biopsies performed in this cohort of post LT children (median age 1.34 years, range 0.65-11.4 years), 20 (10%) presented isolated cholangiolar proliferation and underwent a PTC after a median time of 9.2 months (average: 2-90.7 months) following LT. All patients had received a left lateral segment from deceased donors. Among them, a tight biliary stricture was confirmed in 17/20 (85%) and was managed by balloon dilatation. Serum conjugated bilirubin and bile acid were normal in 10 (58%) and 4 (24%) patients respectively. The median diameter of the intrahepatic bile ducts on USS was 2.75 (2-4 mm), and was >2 mm in 7/17 (42%) following a median follow up of 2.8 years, liver function tests were entirely normal in 15/17 (88%) patients.

**Conclusions:** Biochemical tests and abdominal ultrasound are insufficiently accurate to detect a biliary problem. In our experience any degree of isolated cholangiolar proliferation detected on cytokeratin-7 stained per-cause biopsies was highly sensitive to predict a biliary stenosis at PTC. Biliary features on liver biopsy should lead to a more aggressive approach to unveil biliary strictures. Further studies are needed to disclose the contribution of subclinical biliary obstruction to long-term graft dysfunction and failure in pediatric LT recipients.

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Comparison of outcome in post-transplant lymphoproliferative disorder after paediatric small bowel versus isolated liver transplantation in a single tertiary transplant centre

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Objectives and Study: Post-transplant lymphoproliferative disorder (PTLD) is a major complication in paediatric solid organ transplantation (SOT). Incidence is highest in the small-bowel transplant (SBTx) population most likely because of the high density of lymphoid tissue in the transplanted graft combined with greater immunosuppression. We postulate that PTLD developing in SBTx patients is also likely to be more aggressive and associated with poorer outcomes as compared to liver transplant (LTx) patients. This study aims to compare the characteristics and outcome of PTLD presenting in paediatric SBTx versus LTx patients at a single tertiary transplant centre.

Method: A retrospective review of all paediatric SBTx and LTx patients diagnosed with PTLD since the start of our transplant program from 1989 to 2016 was carried out. PTLD was diagnosed based on World Health Organisation histologic criteria. Treatment protocol for PTLD consisted of reduction of immunosuppression (RIS), rituximab (RTX, included since 2000), cytotoxic T-lymphocyte (CTL) therapy (available on a research basis in 1999-2014 and since 2011 as approved treatment), and chemotherapy.

Results: Total of 37 patients were diagnosed with PTLD during the study period, 23 had LTx and 14 had SBTx with or without combined LTx. Incidence of PTLD was 15% in SBTx and 2.5% in LTx. The SBTx recipients were older than the LTx group at time of transplant (26 vs 13 months, p=0.038), and the majority of LTx were still less than 2 yrs when they developed PTLD (86% vs 52%, p=0.038). There was no difference in recipient EBV seronegative status (91% vs 81%, p=0.461) between SBTx and LTx patients. The median interval from transplant to PTLD was 7 months (range: 2 - 27) in the SBTx group and 6 months (range: 2 - 107) in the LTx group. Higher incidence of acute rejection (79% vs 57%, p=0.173), monomorphic histologic subtype (64% vs 43%, p=0.214), and tumour involvement of transplanted allograft (64% vs 39%, p=0.138) were observed in the SBTx group, although not statistically significant. In both SBTx and LTx groups respectively, majority of tumours were B-cell origin (93% vs 96%, p=0.740) and Epstein-Barr virus (EBV) positive (92% vs 95%, p=0.724) on histology. RTX, CTL and chemotherapy were given in 64%, 29% and 14% of the SBTx patients respectively, and 35%, 26% and 4% of the LTx patients respectively (p=NS). RIS alone resulted in PTLD remission in 50% of LTx patients but in none of the SBTx patients (p=0.002). Overall remission rate was lower in the SBTx group (57% vs 96%, p=0.004). SBTx group was also associated with poorer survival rates at 2 years (46% vs 91%, p=0.003) and 5 year (39% vs 90%, p=0.002). Survival did not differ in either SBTx or LTx groups between pre-RTX (before 2000) and RTX (post-2000) treatment eras, however a trend towards improved survival was observed in SBTx patients during the years when CTL therapy was available (Figure).
[Survival analysis of PTLD in SBTx and LTx groups, stratified into CTL and non-CTL treatment eras.]

**Conclusion:** PTLD in paediatric SBTx patients is associated with more aggressive disease and poorer survival rates as compared to LTx patients. RIS alone in SBTx is insufficient to induce remission of PTLD, and prompt escalation of treatment to CTL (if available) and/or RTX is recommended.

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**HEPATOLOGY - Basic science**

H-O-034

**Toxicological evaluation of a gene therapy approach for the treatment of Crigler-Najjar in rhesus macaques**

Jenny Greig¹, Roberto Calcedo¹, Lety Kuri¹, Jayme Nordin¹, Jessica Albrecht¹, Erin Bote¹, Tamara Goode¹, Edward Chroscinski¹, Peter Bell¹, Laura Richman¹, John Gray², Michael Betts¹, James Wilson¹

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²Audentes Therapeutics, San Francisco, United States

**Objectives and Study:** Crigler-Najjar syndrome (CN) is a rare autosomal recessive disorder of bilirubin metabolism. Mutations in uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) result in the partial or complete absence of enzyme activity, leading to hyperbilirubinemia and jaundice. This study evaluated the potential toxicity of a gene therapy approach for the treatment of CN in rhesus macaques.

**Methods:** AAV8-TBG-hUGT1A1 (AT342), which expresses the human version of UGT1A1 from a liver specific promoter, was infused intravenously into three wild type rhesus macaques at either 1.0x10¹³ genome copies [GC]/kg or 2.5x10¹³ GC/kg. An additional two animals received vehicle only as a control. Throughout the study duration, liver transaminases and peripheral T-cell responses to the AAV8 capsid and the hUGT1A1 transgene were measured by IFN-γ enzyme-linked immunospot (ELISPOT). A liver biopsy was performed at day 28. IFN-γ ELISPOTs were also performed on lymphocytes isolated from bone marrow, spleen, and liver at the time of necropsy (day 56). At necropsy, tissues were harvested for a comprehensive histopathological examination.

**Results:** All rhesus macaques survived until their scheduled necropsy at day 56 with no clinical abnormalities noted. By histopathological analysis, all macaques administered with vector had minimal to mild mononuclear cell infiltration within the portal areas of the liver. There were elevations in ALT and AST levels in individual vector-treated macaques (ALT &LT; 300 U/L, AST &LT; 125 U/L). Specific immune responses against the human UGT1A1 transgene expressed by the vector could be stratified into one of three dose-independent categories: a) positive response to the transgene in the periphery only, i.e. isolated peripheral blood mononuclear cells, b) positive response to the transgene in the liver only, and c) positive response in both the periphery and liver. The immunological observations were not dose-dependent. A liver biopsy was performed at day 28 and expression of hUGT1A1 was evaluated by vector-specific hUGT1A1 RNA quantification and in situ hybridization (ISH), revealing a clear dose response in vector-derived hUGT1A1 RNA.

**Conclusion:** By evaluation of this clinical candidate gene therapy vector in a large animal model, we were able to extensively study expression of hUGT1A1, toxicology, and the immune responses in the periphery and liver following vector administration. The studies support ongoing clinical investigation of AT342 for the treatment of Crigler-Najjar syndrome.

**Disclosure of interest:** J.M. Wilson is an advisor to REGENXBIO, Dimension Therapeutics, and Solid Gene Therapy, and is a founder of, holds equity in, and has a sponsored research agreement with REGENXBIO and Dimension Therapeutics; in addition, he is a consultant to several biopharmaceutical companies and is an inventor on patents licensed to various biopharmaceutical companies. J. Gray and M. Betts are employees of Audentes Therapeutics.
HEPATOLOGY - General Hepatology

H-O-035

Hepatitis C virus infection in 663 European children, results of a web-based survey

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2UCL Great Ormond Street Institute of Child Health, London, United Kingdom

Objectives and Study: The main aim of the present collaborative study was to characterise a population of children (aged ≤18 years) with chronic hepatitis C virus (HCV) infection in follow up in 50 European paediatric centres in 2016 and to investigate current policies around monitoring and treatment.

Method: A web-based REDCap survey was sent to named clinicians in 50 centres across Europe within the PENTA Hep consortium that covers the networks of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Infectious Diseases.

Results: Thirty-six centres (72%) completed the survey, providing data on 663 children with chronic HCV infection (M 319; 48%); 332 children (50.5%) were aged 12 years or more. HCV genotype 1 was the most common (n 380; 57.3%), followed by genotype 3, 4 and 2 [n 127 (19.2%); n 69 (10.4%); n 34 (5.1), respectively; unknown n 49 (7.4%)]. The main route of HCV acquisition was through vertical transmission (n 595; 89.7%). Twenty-two children (3.3%) acquired the infection nosocomially or through unsafe blood product transfusions while the route of acquisition was unknown in 46 (6.9%). Only 4 children (0.6%) were co-infected with human immunodeficiency virus, none with hepatitis B virus. Most children were treatment-naïve (n 425, 64.1%) and 161 were treatment-experienced (24.3%). In 2016, 35 children (5.3%) received treatment with pegylated-interferon and ribavirin, with a further 42 (6.3%) treated with direct-acting antiviral drugs. Data regarding monitoring and treatment policies are summarized in the Table.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you use transient elastography?</td>
<td>72%</td>
<td>28%</td>
<td>-</td>
</tr>
<tr>
<td>Would you use direct-acting antivirals active against HCV, if available, for children aged:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5 years</td>
<td>42%</td>
<td>36%</td>
<td>22%</td>
</tr>
<tr>
<td>6-11 years</td>
<td>78%</td>
<td>19%</td>
<td>3%</td>
</tr>
<tr>
<td>12-18 years</td>
<td>94%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Would you perform a liver biopsy…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in a 6 years old patient</td>
<td>11% / 86% / 1%</td>
<td></td>
<td>14% / 86% / 0</td>
</tr>
<tr>
<td>in a 14 years old patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with normal ALT (yes / no / don't know)</td>
<td>31% / 69% / 0</td>
<td></td>
<td>33% / 64% / 1%</td>
</tr>
<tr>
<td>with raised ALT (yes / no / don't know)</td>
<td>42% / 56% / 3%</td>
<td></td>
<td>47% / 53% / 0</td>
</tr>
</tbody>
</table>

Discussion: The present study provides an up-to-date information on the current epidemiology of HCV infection in children in Europe. The clinical and therapeutic approach to children with chronic HCV infection varied markedly across Europe and is likely to change with the approval of direct-acting antivirals.

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Objectives and Study: Lysosomal acid lipase deficiency (LAL-D) is a rare, progressive disease characterized by accumulation of cholesteryl esters and triglycerides in the liver that leads to dyslipidemia, hepatomegaly, and liver cell damage. Sebelipase alfa (SA) is a recombinant human LAL indicated for the treatment of LAL-D.

Methods: In this multicenter, open-label study, eligible patients >8 months of age were given SA 1 mg/kg by IV infusion every other week for up to 96 weeks. Dose escalation to 3 mg/kg every other week and subsequently to 3 mg/kg weekly was allowed for patients who met protocol-defined criteria; dose reductions for tolerability were permitted to 0.35 mg/kg every other week. Reported here are effects on liver parameters at 96 weeks of SA exposure.

Results: A total of 31 patients were enrolled; median age was 12 y (range 3-55 y). Two patients (6%) had a prior liver transplant. No inferential statistical analyses were conducted as part of this study. Clinical characteristics at Baseline and Week 96 are provided in the table. Marked reductions in ALT and AST were observed. Liver fibrosis improved or did not progress in 7 of 13 patients (54%) with pairwise samples at Baseline and Week 96 and with Baseline Ishak stage of 0-5. Three patients had a ≥1-point reduction in Ishak stage, including 2 patients who had a ≥2-point reduction. One of 3 patients with Baseline stage of 6 and a pairwise sample at Week 96 improved to stage 2. SA was generally well tolerated. Most adverse events (AEs) were mild to moderate in severity. Three patients (10%) experienced infusion-associated reactions that were at most mild (n=2) or moderate (n=1) in severity. There were no discontinuations due to AEs. Two patients (6%) were positive for anti-drug antibodies on 1 occasion each; neither developed neutralizing antibodies.

Conclusion: Long-term treatment with SA was well tolerated and resulted in sustained improvements in markers of liver injury in this diverse population of patients with LAL-D.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Week 96</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, IU/L</td>
<td>63.5</td>
<td>34.0</td>
<td>-44.4</td>
</tr>
<tr>
<td>ALT &gt;1.5xULN, n (%)</td>
<td>19/31 (59)</td>
<td>5/27 (19)</td>
<td></td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>65.5</td>
<td>42.0</td>
<td>-38.4</td>
</tr>
<tr>
<td>AST &gt;1.5xULN, n (%)</td>
<td>15/31 (48)</td>
<td>2/27 (7)</td>
<td></td>
</tr>
<tr>
<td>UK-MELD score</td>
<td>46.5</td>
<td>45.3</td>
<td>-0.6</td>
</tr>
<tr>
<td>Fibrosis, n (%) #</td>
<td>20/30 (67)</td>
<td>12/17 (71)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, n (%) #</td>
<td>8/30 (27)</td>
<td>4/17 (24)</td>
<td></td>
</tr>
<tr>
<td>Liver volume, MN</td>
<td>1.4</td>
<td>1.2</td>
<td>-17.6</td>
</tr>
<tr>
<td>Liver fat content, %</td>
<td>8.1</td>
<td>6.5</td>
<td>-14.9</td>
</tr>
<tr>
<td>Spleen volume, MN</td>
<td>2.6</td>
<td>2.2</td>
<td>-16.5</td>
</tr>
</tbody>
</table>

N=31, unless otherwise noted; results are medians. MN=multiples of normal. #Fibrosis=Ishak score of 1-4; cirrhosis=Ishak score of 5-6.

[Clinical characteristics at Baseline and Week 96]
Disclosure of interest: BB has received funding for clinical studies from Alexion, BioMarin, Shire, Genzyme, ArmaGen, and Ultragenyx; funding for independent research from BioMarin and Shire and consulting fees/honoraria from ArmaGen, BioMarin, Shire, Alexion, Genzyme, and Regenxbio. ACS has received funding for clinical studies and honoraria for scientific presentations from Alexion. MK has received funding for clinical studies from Alexion. KA and FA are employees of Alexion and may own stock/stock options.
Determination of ATP7b in Golgi apparatus in patients with Wilson disease and non-alcoholic steatohepatitis - preliminary results

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¹The Children's Memorial Health Institute, Warsaw, Poland

Objectives and Study: Histopathological evaluation of liver biopsies patients with Wilson’s disease (WD) is difficult and uncharacteristic due to the similar changes (i.e. hepatocellular ballooning, fatty degeneration, inflammatory infiltration) observed in other conditions, especially non-alcoholic steatohepatitis (NASH). Previous genetic and in vitro studies have allowed to determine the mutation of the ATP7b (cooperative transport P-type ATPase) protein in WD. However, there are no studies on the expression of ATP7b in WD patients. The aim of the study was to determine localization of ATP7b in relation to golgin 97 - the protein of Golgi apparatus and endosomes in the liver biopsies of patients with WD and NASH using the confocal microscopy technique.

Method: The archival paraffin embedded liver biopsies of WD patients with p.H1069Q mutation (n=6) and NASH patients (n=3) from the Department of Pathology of The Children's Memorial Health Institute were used. The paraffin blocks were cut (4 µm), mounted on silanized microscope slides and deparaffinized. After antigen retrieval (citric buffer pH 6, 98 °C 30 min.) and nonspecific signal blocking with 5% goat serum samples were stained with the specific sets of antibodies: rabbit anti- ATP7b (LifeSpan BioSciences), mouse anti-golgin 97 (Abcam), goat anti - rabbit Alexa Fluor 633 (Invitrogen by Thermo Fisher Scientific), goat anti - mouse Alexa Fluor 488 (Invitrogen by Thermo Fisher Scientific). Counterstaining of cell nuclei with DAPI (Molecular Probes by Life Technologies) were done. Localization of proteins and quantitative analysis were done on FV-1000 (Olympus) confocal microscopy. For evaluation were chosen hepatocytes without fatty degeneration. The study was approved by a local Ethics Committee.

Results: Differences in the location of ATP7b and golgin 97 in both groups were possible to determine using 3D pictures. In WD patients both ATP7b and golgin 97 occurred in hepatocytes in the form corresponding to the shape and location of Golgi apparatus. In NASH patients, the signal of both proteins was much more diffuse and was located in the area corresponding to Golgi apparatus, endosomes and cell membrane of hepatocytes. Image analyses showed that co-localization of both proteins was much more pronounced in patients with WD than with NASH. This indicates a decrease in the occurrence of ATP7b protein outside the Golgi apparatus in case of WD disease.

Conclusion: Our preliminary results show that co-localization analyses of ATP7b and golgin 97 could be a novel method helping in differentiation between WD and NASH patients. The study was financed by the Children's Memorial Health Institute Grant No. 246/17.

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Salivary markers in hepato-metabolic complications of pediatric obesity

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²Theoreo srl, Montecorvino Pugliano (SA), Salerno, Italy

**Objectives and Study:** Obesity represents one of the major causes of morbidity at all age groups including pediatrics, with a parallel increase in the incidence of its complications. To assess the diagnostic role of salivary markers (uric acid, insulin, glucose) for the non-invasive screening of obesity related hepato-metabolic abnormalities in pediatric patients, namely metabolic syndrome (MetS) and Non-Alcoholic Fatty Liver Disease (NAFLD).

**Method:** We recruited for our pilot case-control study 41 subjects [23 obese and 18 normal weight (NW) healthy controls] characterized on the basis of medical history, clinical, anthropometric and laboratory data. MetS was characterized by waist circumference >95th%ile; triglycerides >150 mg/dl; glucose >100 mg/dl; systolic blood pressure >95th%ile; HDL cholesterol < 40 mg/dl. Liver involvement, defined on the basis of ultrasonographic liver brightness, allowed to allocate patients into 2 groups: obese with ([St+], n=15) and without ([St-], n=8) hepatic steatosis. A saliva sample from each subject was collected by Salivette® and analyzed by GC-MS to measure the uric acid (UA) and glucose levels and HPLC-MS/MS for insulin levels.

**Results:** Serum and salivary levels of UA (p=0.016; R²=0.016), insulin (p< 0.0001; R²=0.79) and homeostatic model assessment-insulin resistance index (HOMA-IR) (p< 0.0001; R²=0.79) showed a statistically significant correlation. Their values tended to be higher in obese pts compared to NW controls [UA (4.8±1.15 OB vs 4.0±0.76 NW mg/dl and 157±13.8 OB vs 143.5±4.35 µM NW, respectively); INS (22.6±9.7 OB vs 10.3±5.2 NW µU/ml and 19.6±8 OB vs 5.8±2.8 NW nM, respectively); HOMA (4.3±2.3 OB vs 2.0±1.2 NW and 358.2±215.3 OB vs 119.7±73.9 NW)] prevalently in obese subjects with steatosis (+) in both biological fluids. The same statistically valid correlation exists between serum and salivary glucose levels (p< 0.0001; R²=0.62), without differences between [St+] and [St-] subjects (p=0.18; r = 0.04). Notably, UA and insulin levels increased in both fluids proportionally to the number (n = 0, 1, 2, ≥ 3) of Metabolic Syndrome (MetS) components (Table 1.).

<table>
<thead>
<tr>
<th>Blood uric acid levels (mg/dL)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood insulin levels (mg/dL)</td>
<td>10.4±5.1</td>
<td>19.9±11.3</td>
<td>23.4±10.1</td>
<td>27.8±4.8</td>
</tr>
<tr>
<td>Salivary uric acid levels (µM)</td>
<td>143.8±4.6</td>
<td>151±13.9</td>
<td>159.1±10.5</td>
<td>159.1±16.1</td>
</tr>
<tr>
<td>Salivary insulin levels (µM)</td>
<td>5.9±2.9</td>
<td>18.3±8.9</td>
<td>20.9±9.9</td>
<td>21.8±4.1</td>
</tr>
</tbody>
</table>

**Conclusion:** Our preliminary results indicate that salivary UA is a valuable surrogate of uricaemia. Salivary insulin is a significant marker of early stages of MetS as a disease marker. Salivary HOMA-IR could be a good substitute of the serum index for identifying insulin resistant subjects. Further and larger study are warranted to confirm its value to individuate noninvasively obese children at risk of MetS and fatty liver.
Rapid diagnosis of Wolman disease is possible by consideration of characteristic primary symptoms

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Objectives and Study: Wolman disease is a rare autosomal recessive inborn error of metabolism. It represents the most severe manifestation of lysosomal acid lipase deficiency. The defect in lipase activity leads to accumulation of large amounts of lipids in the liver, spleen, gut and many other tissues. Most infants die within the first months of life and no child survives more than 2 years. However, the development of the enzyme replacement therapy with sebelipase alfa (Kanuma) has shown extraordinary success. Long term treatment has shown excellent physical and neurological outcome of patients with Wolman disease. Many of them live a relatively normal life. Therefore, early diagnosis of this highly life threatening disease is crucial. Many clinical signs and symptoms of the disease are well known. However, the very first symptoms of the disease have not been defined.

Method: Patients with Wolman disease were collected via personal communication with neonatal or metabolic centers. Medical reports and medical charts were analysed according to clinical, biochemical and outcome parameters. If possible families were additionally phoned for a short telephone interview.

Results: Eight infants with Wolman disease were identified. All patients were born before enzyme replacement therapy was available. The clinical presentation is shown in table. Three families were phoned and asked about the first symptoms. Notably, in all cases the first symptom were drinking weakness and vomiting after meal. One child was admitted on the day of birth due to a brother who died because of Wolman disease. This child showed normal blood results but had multiple vacuolated leucocytes (see table, patient 7).

All patients died within the first 7 months, three of them after stem cell therapy.
<table>
<thead>
<tr>
<th>Patient</th>
<th>First symptoms on day</th>
<th>First symptoms</th>
<th>Transaminases, Cholesterol, Hemoglobin at first blood test (day 12-55)</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Drinking weakness, vomiting, abdominal distension</td>
<td>Normal transaminases, no anemia, LDL elevated, HDL normal</td>
<td>Adrenal calcification, splenomegaly, normal liver</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Drinking weakness, vomiting, abdominal distension</td>
<td>Normal transaminases, no anemia, LDL normal, HDL normal</td>
<td>Adrenal calcification, splenomegaly, normal liver</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>Drinking weakness, vomiting after meal, abdominal distension, fever</td>
<td>Normal transaminases, mild anemia</td>
<td>Adrenal calcification, normal spleen, normal liver</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>Drinking weakness, vomiting, abdominal distension</td>
<td>Normal transaminases, no anemia, LDL, HDL normal</td>
<td>Adrenal calcification, splenomegaly, normal liver</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>Drinking weakness, vomiting</td>
<td>Normal transaminases, no anemia, LDL, HDL normal</td>
<td>Adrenal calcification, normal spleen, normal liver</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>Drinking weakness, vomiting</td>
<td>Normal transaminases, no anemia, LDL elevated, HDL normal</td>
<td>Adrenal calcification, splenomegaly, hepatomegaly</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>Drinking weakness, vomiting, abdominal distension</td>
<td>Mild elevation of transaminases, mild anemia</td>
<td>Adrenal calcification, splenomegaly, normal liver</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Drinking weakness, vomiting</td>
<td>Normal transaminases, no anemia, LDL normal, HDL normal</td>
<td>Adrenal calcification, splenomegaly, normal liver</td>
</tr>
</tbody>
</table>

[Biochemical and sonographic presentation]

**Conclusion:** In contrast to the current knowledge about Wolman disease the first signs and symptoms are not hepatic. At the very beginning patients with Wolman disease have normal or near normal transaminases, normal liver synthesis and usually no hepatomegaly. They are born healthy and symptoms begin on day 5-35 with drinking weakness and vomiting and abdominal distension. Together with the specific sign of adrenal calcification a rapid suggestion of Wolman disease is possible. As sensitive and specific enzymatic testing for lipase activity is available infants can easily be treated early in life before multiorgan failure begins.

**Disclosure of interest:** The first author received speakers honorarium of Alexion.

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Objectives and Study: Children with Wilson's disease (WD) might develop simple steatosis, steatohepatitis or severe fibrosis. Hepatic steatosis and fibrosis can be non-invasively quantified using transient elastography (TE; Fibroscan). Interestingly, liver steatosis in WD is often present, even if the disease is successfully treated. Our previous analyses (Krawczyk / Lammert, Hepatology 2017) demonstrated that TE can be used as a reliable phenotyping tool allowing identification of genetic modifiers of liver injury. Here we investigated the association between critical prosteatotic and profibrotic gene variants and the degree of liver fibrosis and steatosis in children with WD.

Method: We included 56 children (mean age 7.9 yrs, range 2.5-17 yrs, 30 girls) with Wilson's disease, treated with either zinc or D-penicillamine for the mean period of 4.1 years with clinical and laboratory improvement. All patients underwent TE (Fibroscan, Echosens, France) examinations with medium (M) probe to assess liver stiffness (LSM) and steatosis (Controlled Attenuation Parameter, CAP). Subsequently, we genotyped the PNPLA3 p.I148M, TM6SF2 p.E167K and MBOAT7 rs6417389 variants, which have been associated with liver steatosis and fibrosis (Anstee / Day, Gastroenterology 2016).

Results: Reliable TE measurements were obtained in all patients with WD. They presented with normal median liver stiffness (5.3 kPa, range 2.4-14.3 kPa) and elevated liver steatosis, as reflected by a median CAP = 248 dB/m (range 160-363 dB/m). Genotype distributions were consistent with Hardy-Weinberg equilibrium (all P > 0.05 by exact test). Among the tested variants, we detected a significant association between the TM6SF2 risk allele and increased CAP (P = 0.029, dominant model) in WD. Neither the PNPLA3 nor the MBOAT7 polymorphisms were associated with hepatic steatosis, and none of the variants affected liver fibrosis in this cohort (all P > 0.05).

Conclusion: Persistent steatosis after successful pharmacological treatment in Wilson's disease is a frequent condition. This phenotype seems to be particularly common among patients carrying the TM6SF2 p.E167K risk allele. Given the potential harmful effects of liver steatosis, we recommend timely follow up of liver phenotypes in pediatric patients with Wilson's disease, even after copper depletion, to allow the early detection of disease progression.

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**Baseline IgG, AIH score and IL2 can predict subsequent biochemical remission in paediatric autoimmune hepatitis**

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**Objectives and Study:** Although autoimmune hepatitis (AIH) can be treated with corticosteroid-based first-line therapy, incomplete remission is associated with progressive liver fibrosis. So far accepted predictors of the subsequent biochemical remission of AIH patients are lacking. In an earlier study with adult AIH (aAIH) patients we could identify dysregulated iron homoeostasis and lower IgG titres as predictors for biochemical remission (BR).

**Method:** We retrospectively analysed baseline parameters, including AIH scores, IgG titres, iron homeostasis and cytokine levels, in 60 children with biopsy proven paediatric AIH (pAIH), diagnosed between 1993 and 2015. Children with AISC, replicative viral hepatitis, an AIH score below 10 and bacterial infections at diagnosis were excluded from the study. BR was defined as persistent age-specific normalization of AST, ALT and IgG levels on first line therapy. Incomplete remission (IR) was defined as improvements in ALT, AST and IgG without normalization after at least 24 months and/or change to second line therapy. IR was not necessarily associated with switch to second line therapy. First line therapy was based on international recommendation with 0.1mg/kgBW/d prednisolone and with 1-2mg/kgBW/d azathioprine. For the identification and validation of predictive parameters our cohort was split into a training cohort (diagnosis until 2010) and a validation cohort (diagnosis since 2010).

**Results:** Of 60 analyzed pAIH patients 50 reached following endpoints: BR (N=23); IR (N=21) and liver transplantation (LTX; N=6). Nine of 21 patients with IR were switched to 2nd line therapy (Ciclosporin N=6, Mycophenolate Mofetil N=1, Infliximab N=1, Everolimus N=1). Baseline immunoglobulins were significant lower in pAIH children with subsequent BR. Cut off values for IgG>1.35 ULN for baseline IgG (AUROC 0.667) and AIH score > 16 (AUROC 0.762) could predict IR+LTX with a specificity of 0.5 and a sensitivity of 0.89. Lower AIH scores (≤16 points) could predict BR in our training and validation cohorts. Furthermore higher baseline IL-2 and MCP-1/CCL2 levels were associated with BR in a sub-cohort (N=38) and a combined score of IL-2 level (&LT; 10.8 µg/ml=1 point, >10.8 µg/ml=0 points) and simplified AIH score (>6=1 point, ≤6=0 points) predicted treatment response most precisely (AUROC 0.759; specificity=0.74; sensitivity=0.72). In contrast to adults, elevated serum markers indicating iron overload were not commonly found in pAIH children and were not associated with the subsequent treatment response in pAIH.

**Conclusion:** The baseline AIH score and IgG could be validated as a predictor of treatment response. Furthermore a score of simplified AIH score and IL-2 levels showed highest AUROC and specificity for predicting IR+LTX. Low baseline IL-2 may help identify children who need salvage therapy. This could be important because the use of low-dose IL-2 therapies is being tested in various autoimmune diseases.

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Pregnancy in ladies with autoimmune hepatitis diagnosed during childhood and long-term treated with immunosuppressive drugs

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Objectives and Study: Pregnancy in the course of autoimmune hepatitis (AIH) is associated with maternal and foetal complications such as early miscarriages, prematurity, low birth weight, caesarean delivery and relapse of the liver disease. Underlying cirrhosis is reported as a major risk factor for pregnancy complications. Relapses occur especially in the post-partum period and are associated with impaired AIH control and discontinuation of treatment. Prednisone and azathioprine (AZA) represent the first-line treatment for AIH. AZA is used to maintain remission and avoid hepatic flares and is reported as safe during pregnancy.

Methods: An observational study was retrospectively conducted by patients' chart review from 1990 to 2017. Seven pregnancies occurred between 2010 and 2017 in six young ladies previously diagnosed and treated as paediatric patients for AIH. The median follow-up time from the disease onset was 24.3 years (range 18.8 - 27.8 years) and the median follow-up from the beginning of the first pregnancy was 0.8 years (range 0.1 - 7.1 years).

Results: The median age at AIH onset and at the end of follow-up was respectively 9.3 years (range 2.3 - 14 years) and 32.5 years (range 23.5 - 38.3 years). The median age at the onset of first and second pregnancy was respectively 29.1 years (range 22.8 - 37.9 years) and 35.5 years (range 34.6 - 36.4 years). Two patients had AIH - autoimmune sclerosing cholangitis overlap variant (AOV), three AIH type 2 and one AIH type 1. Patients were treated with prednisone, azathioprine and ursodeoxycholic acid (UDCA); three patients also received cyclosporine as second-line therapy. At the beginning of pregnancy all patients were in clinical and biochemical remission with a mean elastography value at last follow-up visit of 6.4 kPa (range 3.7 - 10.3 kPa). During pregnancy five patients continued to receive treatment with AZA and UDCA while a patient was out of therapy since 5 years and 9 months. No relapse occurred during pregnancies in all patients. Abnormal serum GGT was observed in a patient with AOV. No side effects related to AZA treatment were recorded. In a patient, a biochemical relapse occurred one year after delivery when AZA was discontinued. This relapse promptly responded to prednisone and AZA reintroduction. Four full-term healthy neonates were born without complications. One baby was born late preterm (36+4 weeks), appropriate for gestational age, from a spontaneous labour induced for reduced foetal movements. The other two pregnancies are still ongoing without complications. One miscarriage was recorded during the first trimester of pregnancy in a patient with AIH type 1 while on treatment with AZA.

Conclusions: Pregnancy with good maternal and neonatal outcomes is possible for women diagnosed in paediatric age for AIH and long term treated with immunosuppressive therapy. Azathioprine maintains remission and avoids relapse during pregnancy with a good safety profile.

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Abnormal glycosylation and wilson-like liver disease: Three new cases of TMEM199-deficiency

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Objectives and Study: Congenital disorders of glycosylation (CDG) are a family of genetic diseases that include subtypes with a predominant or isolated liver involvement which may sometimes mimic hepatic Wilson-disease. Deficiency of TMEM-199, a chaperone in the synthesis of the V-ATPase acidifying vesicles of the Golgi secretory pathway, is characterized by an exclusive/predominant hepatic presentation. There is no information on the long-term outcome in this disorder.

Methods: We present the long-term follow-up of two children (patient #1 and #2) diagnosed to have hepatic CDG about 20 years ago, and clinical/laboratory features of one unrelated child (#3), all having recently been identified with TMEM199-deficiency.

Results: Clinical examination was silent. The clinical and biochemical findings (Table) were consistent between the patients and included: pathological glycoprotein synthesis, low ceruloplasmin, hypertransaminasemia, hypercholesterolemia, vitamin D-resistant high alkaline phosphatase and creatine phosphokinase, modest increase of liver copper, mild non-progressive liver fibrosis/steatosis, normal psychomotor development. Wilson-disease and aceruloplasminemia were ruled out by appropriate tests. Transferrin glycosylation was consistent with a CDG type 2. Exome-sequencing identified in all compound heterozygous mutations in TMEM199 (frameshift with a premature stop, and a missense change, respectively). Western Blot analysis showed absence of the TMEM199 protein in patient fibroblasts. The clinical course for all three patients has been stable over two decades.

<table>
<thead>
<tr>
<th>Neurological development</th>
<th>Patient 1 (F) age: 2</th>
<th>Patient 1 (F) age: 27</th>
<th>Patient 2 (M) age: 2</th>
<th>Patient 2 (M) age: 24</th>
<th>Patient 3 (M) age: 1.4</th>
<th>Patient 3 (M) age: 2.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological development</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild delay of speech</td>
<td>Normal</td>
</tr>
<tr>
<td>AST (&lt;41 U/L)</td>
<td>349</td>
<td>53</td>
<td>299</td>
<td>98</td>
<td>656</td>
<td>156</td>
</tr>
<tr>
<td>ALT (&lt;45 U/L)</td>
<td>329</td>
<td>23</td>
<td>221</td>
<td>50</td>
<td>437</td>
<td>104</td>
</tr>
<tr>
<td>ALP (&lt;475 U/L)</td>
<td>1995</td>
<td>1140</td>
<td>3990</td>
<td>903</td>
<td>1235</td>
<td>713</td>
</tr>
<tr>
<td>CPK (&lt;170 U/L)</td>
<td>799</td>
<td>561</td>
<td>442</td>
<td>1428</td>
<td>510</td>
<td>204</td>
</tr>
<tr>
<td>Ceruloplasmin (20-46 mg/dL)</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>8.4</td>
</tr>
<tr>
<td>Liver Ultrasonography</td>
<td>Bright liver</td>
<td>Bright liver</td>
<td>Bright liver</td>
<td>Normal</td>
<td>Bright liver</td>
<td>Bright liver</td>
</tr>
<tr>
<td>Liver Histology</td>
<td>Mild periportal fibrosis; focal steatosis</td>
<td>Mild periportal fibrosis; focal steatosis</td>
<td>Not done</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Copper (&lt;50 µg/g dry weight)</td>
<td>318 µg/g</td>
<td>250 µg/g</td>
<td>Not done</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Our patients are affected by a recently described rare congenital disorders of glycosylation mimicking Wilson-disease and presenting with chronically elevated transaminases, low serum ceruloplasmin and copper, caused by mutations in gene encoding transmembrane protein TMEM199. The disease appear to have a benign long-term course. The mechanisms potentially involve at least partial loss of either or both of the copper transporting proteins ATP7A and ATP7B.
Why TMEM199-deficiency causes liver disease only is enigmatic, since the loss of V-ATPase *per se* causes a more widespread phenotype.
Does low gamma-glutamyl transferase levels at presentation in Biliary atresia predict a poor outcome?

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Objectives and Study: Biliary atresia (BA) is a progressive obliterative cholangiopathy leading to cholestasis, fibrosis and cirrhosis. Gamma glutamyl transferase (GGT) levels are typically elevated in BA. Although there are anecdotal reports of BA patients presenting with normal GGT levels, this cohort has not been described previously. Further, the role of initial GGT as a predictor of outcome in BA has not been investigated. Our objectives are to describe patients with BA with a normal GGT level at diagnosis and compare them with high GGT BA group.

Method: A retrospective audit of all patients with a diagnosis of biliary atresia from 2000-2017, in a single paediatric liver transplant centre was conducted. The demographics, liver biochemistry at presentation, age at diagnosis and at Kasai Portoenterostomy (KPE) were recorded. The patients were divided into normal and high GGT BA group by calculating the mean of three consecutive GGT values obtained at initial presentation and prior to KPE. Normal GGT level was defined as mean GGT of < 200IU/L and < 40IU/L in children less than and more than 3 months of age respectively. The two groups were compared with regard to several variables including median age at diagnosis, median age at KPE, presence of biliary atresia splenic malformation (BASM), median time to clearance of jaundice and outcome. Clearance of jaundice was defined as two consecutive values of total bilirubin < 20µmol/L. Outcome was defined as survival with native liver, liver transplantation and death.

Results: 112 patients were noted to have a diagnosis of BA confirmed by histology and intraoperative findings between January 2000 and October 2017. Of these, 19 patients were excluded as they had had their KPE performed in another centre, and were referred for transplantation. Of the 93 patients included in the final analysis, 10 patients had normal GGT levels. There was no significant difference between the normal GGT and high GGT group in gender, median age at diagnosis or median age at KPE. BASM, known to be associated with a poorer outcome, was present in 6% of the high GGT group, but in none of the low GGT group. In comparison with high GGT group, the normal GGT group showed a trend towards delayed clearance of jaundice (122 days vs 62 days, p=0.09), shorter time from KPE to liver transplantation (6 months vs 14 months, p=0.08) and younger age at liver transplantation (8 months vs 15 months, p=0.07). K-M curves were suggestive of poorer transplant-free survival in patients with normal GGT levels at presentation (p=0.378).
Conclusion: 10.7% of patients with biliary atresia had normal GGT levels at presentation. Although, it did not assume statistical significance, the normal GGT BA group took twice as long to clear jaundice, required transplantation earlier and had poorer transplant-free survival than the high GGT BA group. These results need confirmation with larger studies and we are currently expanding our audit to include a larger cohort.

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The influence of single nucleotide polymorphism of TLR4 gene on cytokine profile in children with nonalcoholic fatty liver disease

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Objectives and Study: To evaluate the role of toll-like receptor 4 (TLR4) gene polymorphism in children with nonalcoholic fatty liver disease (NAFLD). We examined 55 children, the average age of patients was (12.08 ± 2.71) years. All patients and their parents had given their agreement to participation in the study.

Method: Fifty five subjects (35 - with NAFLD, 20 - without steatosis) underwent polymerase chain reaction and restriction fragment length polymorphism to assess one single nucleotide polymorphism in the TLR4 gene (Asp299Gly). The presence of hepatic steatosis was determined by transient elastography using «FibroScan® 502 touch» with the measurement of controlled attenuation parameter (CAP). According to the molecular genetic survey and CAP measurement patients were divided into 4 groups: 1 group consisted of 29 patients with NAFLD and "wild" TLR4 (Asp299Asp) genotype, 2 group consisted of 6 children with NAFLD and TLR4 Asp299Gly polymorphism, 3 group - 18 children without steatosis with the "wild" TLR4 (Asp299Asp) genotype, 4 group - 2 children without steatosis with TLR4 Asp299Gly polymorphism. Interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) quantitative determination were performed with immunoassay.

Results: The frequency of SNP TLR4 (Asp299Gly) detection did not have any significant differences between NAFLD group and children without steatosis (17.1% and 10.0%, respectively). Patients with "wild" genotype TLR4 (Asp299Asp) differed from SNP TLR4 Asp299Gly carriers with higher levels of proinflammatory cytokines - IL-6, TNF-α (p&LT; 0.05). Anti-inflammatory IL-10 remained significantly elevated in NAFLD patients with TLR4 Asp299Gly polymorphism which was combined with lower levels of pro-inflammatory cytokines in contrast to NAFLD patients with a "wild" TLR4 Asp299Asp genotype whose level of IL-10 was significantly reduced (p&LT; 0.05). A direct correlation between SNP TLR4 (Asp299Gly) detection and the level of IL-10 was found (r= 0.459, p&LT; 0.05). Also NAFLD patients with SNP TLR4 (Asp299Gly) did not differ by the average stiffness of liver parenchyma and CAP level compared to NAFLD patients with "wild" TLR4 (Asp299Asp) genotype.

Conclusion: Thus, the course of NAFLD in patients with "wild" TLR4 (Asp299Asp) genotype is accompanied by an increase in pro-inflammatory cytokine production and IL-10 reduction without significant structural differences in the liver parenchyma in comparison with SNP TLR4 (Asp299Gly) carriers. Unlike patients with a "wild" genotype, NAFLD patients with SNP TLR4 (Asp299Gly) are characterized by increased secretion of IL-10 according to levels of proinflammatory cytokines.

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Incidence, clinical features and prognosis of food allergy in children who underwent liver transplantation

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Objectives and Study: Children suffer from food allergy after liver transplant. We evaluated our 16 years of experience in pediatric patients who developed food allergy after liver transplant.

Methods: The clinical and laboratory data and clinical outcome of food allergy was evaluated. Total eosinophil count, total IgE and specific IgE levels were measured and skin prick tests were performed.

Results: There were a total of 236 pediatric patients who were liver transplanted in Başkent University Hospital between 2001-2017 years. Food allergy incidence was 8% (19/236) among all patients with liver transplantation. All of the patients with food allergy were younger than 3 years of age and food allergy incidence at this group of age was 19.2% (19/99). Twelve patients were male (63.2%). The mean age at the time of liver transplant was 7.92±2.64 months. All of the patients were started on tacrolimus in the posttransplant period. The mean period of time from transplantation to food allergy was 14.5±13.6 months. Four patients had single food allergy, while 15 patients had multiple food allergies. The allergen was milk in 3 patients and nut in one patient with single food allergy. The allergens in patients with multiple food allergy were egg (13 patients, 86.7%), milk (11 patients, 73.3%), nuts (6 patients, 40%), wheat (5 patients, 33.3%), lentil (4 patients, 26.7%), chickpea (4 patients, 26.7%), tropical fruits (3 patients, 20%), red meat (2 patients, 13.3%), soybean (2 patients, 13.3%), sesame (2 patients, 13.3%) and fish (1 patient, 6.7%). The presenting symptoms included diarrhea (13 patients, 68.4%), flushing (12 patients, 63.2%), angioedema attacks (9 patients, 47.4%), bronchiolitis/chronic cough (7 patients, 36.8%) and vomiting (6 patients, 31.6%). One patient with multiple food allergy also had anaphylaxis with lentil ingestion. The total eosinophil count and eosinophil percentage in blood at the time of diagnosis for food allergy were 1853±2876/mm³ and 12.7±10.91%, respectively. Twelve patients had eosinophilia. Total IgE count was 350±411 IU/ml. Nine patients had an increase in total IgE. Milk, egg and wheat specific IgEs were positive in 14 (73.7%), 10 (52.6%) and 7 (36.8%) patients, respectively. Skin prick test was positive for specific allergens in 13 (68.4%) patients. The patients were followed up with a mean period of 4.76±3.97 years. All of the incriminated foods were successfully reintroduced in 7 (36.8%) patients, while only some of the foods were successfully introduced in 8 patients with multiple food allergies. Out of 7 patients who have complete resolution of food allergy, 3 had single food allergy (3/4 patients, 75%) and 4 patients (4/15 patients, 26.7%) had multiple food allergy.

Conclusion: The development of food allergy after liver transplantation is common especially in patients who were transplanted under 3 years of age. Multiple food allergies are more common and they are mostly IgE-mediated. Prognosis is better in single food allergies. Also, milk, egg and wheat were more commonly reintroduced than other foods in multiple food allergies.
HEPATOLOGY - Transplantation

H-eP-012

A single center experience of liver-kidney transplantation in children

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Objectives and Study: Pediatric liver-kidney transplant (LKT) is performed in autosomal recessive polycystic kidney disease (ARPKD), primary hyperoxaluria type 1 (PH1) and in less frequent inborn metabolic diseases. We report our experience in pediatric LKT, performed between 2010 and 2017.

Method and Results: A total of 14 patients (10 F) (7%) with median age of 8.9 years (range 1.7-18 yrs) underwent LKT. Indications were ARPKD in 6 patients (42.8%) and PH1 in 7 patients (50%) and methylmalonic academia (MMA) in 1 patient (7%). ARPKD and PH1 patients were on dialysis prior to transplantation, 11 patients (4 PH1, 6 ARPKD and 1 MMA) received simultaneous LKT, 3 patients with PH1 underwent sequential, liver-first, transplantation. Cadaveric LKT was performed in 12 children, using 7 whole livers and 5 partial grafts; sequential living donor LKT (time interval 8 and 20 months) was performed in 2 children with PH1, one from the same donor and one from different donors. In all PH1 patients, hemodialysis was performed during simultaneous LKT to reduce the risk of oxalate deposition in the renal graft. 4 patients (28.5%) had postoperative complications: hemorrhage (n=3) and biliary stenosis (n=1). Hemorrhage complications was seen in patients who received simultaneous LKT. 3 patients (21.4%) had biopsy-proven acute cellular rejection requiring steroids pulse: one renal ACR, 6 months after LKT, and 2 liver ACRs, 3 and 12 months after LKT, respectively. 13 children (92.8%) have good liver and kidney function after a median follow up of 4.5 years (range 0.3-6.5). One patient with PH1 died from acute Budd-Chiari due to early caval thrombosis 8 days after LKT. Patient and graft survivals after LKT for ARPKD and after living donor LKT were 100%. No donor morbidity or mortality were observed. 6 months after LT, MMA patient is in good clinical condition and he had noticeable decreased in serum MMA level.

Conclusion: LKT is effective in children with ARPKD and PH1. Different type of liver grafts, from cadaveric and living donor, can be used with similar excellent results. In PH1 patients, peritransplant emodialysis and a proper choice between combined and sequential LKT is critical to avoid early kidney graft damage

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Donor derived cell free DNA, a noninvasive diagnostic method to detect liver injury in pediatric liver transplant patient

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Objectives and Study: Liver transplantation is the last hope for children with end-stage liver disease. To preserve graft health, accurate and timely diagnosis of allograft injury, such as rejection and optimize immunosuppression use is important. Liver biopsy remains the gold standard for rejection surveillance, but this technique suffers from invasiveness, interobserver variability, and patient discomfort which make it impractical for paediatric group. We proposed donor-derived cell-free DNA (dd-cfDNA) as a new noninvasive marker to monitor graft injury.

Method: We prospectively recruit paediatric patients preparing to receive liver transplant since March, 2015 in National Taiwan University Hospital. Single-nucleotide polymorphisms (SNPs) distributed across the genome was used to discriminate circulating DNA molecules coming from donor part or recipient part. Without doing separate donor and recipient genotyping, we designed targeted panel encompassing 200 SNPs with known high population minor allelic frequency to assess dd-cfDNA in the plasma of transplant recipients by deep sequencing method. Serial dd-cfDNA levels were quantified and dd-cfDNA percentages (dd-cfDNA/total cfDNA) were compared to simultaneous biochemical and histologic results.

Results: Four children who suffered from of biliary atresia, progressive familial intrahepatic cholestasis type 2 and 3 were enrolled. They received liver grafts from their parents at a median age of 4.49 years. Dd-cfDNA percentage was increased to more than 100 times than baseline on day 1 post-transplant indicating reperfusion injury, but rapidly declined in patients without graft injury. In one patient with biopsy-proven acute rejection, the liver function was elevated to 3 times the upper normal limit, and the percentage of dd-cfDNA rose greater than 4-6 times the value of percentage during stable period. In addition, the ascension of dd-cfDNA was 1-month earlier before the peak of the liver function. However, no significant dd-cfDNA elevation was found in a patient with airway viral infection related increased liver function. This result suggested dd-cfDNA may provide independent information predicting graft integrity.

Conclusion: In this study, we demonstrated that dd-cfDNA could detect acute liver injury earlier and more sensitively. It may serve as a hopeful and useful method to efficiently monitor graft health in paediatric group.

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Correlation of cognitive functioning tested by Children’s Colour Trail Testing CTT and PedsQL\textsuperscript{TM} Cognitive Functioning Scale with school performance and parental education in children after liver transplantation

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\textbf{Background:} PedsQL\textsuperscript{TM} Cognitive Functioning Scale (CogPedsQL) and the Children’s Colour Trail Test (CCTT) have previously revealed reduced cognitive functioning in children after liver transplantation (OLT) compared with published controls\textsuperscript{1}. Association of CogPedsQL and CCTT results with familial educational background or school performance has not yet been examined.

\textbf{Aim:} To examine the correlation of CCTT and CogPedsQL results in children after OLT with school performance and familial educational background, in order to differentiate the influence of disease versus the influence of familial educational background.

\textbf{Methods:} 155 children (78f, median age 10.4 (1-18) years; 4.9 (0.1-17) years after OLT) underwent testing for cognitive functioning with either PedsQL\textsuperscript{TM} Cognitive Functioning Scale (child self-report and parent proxy-report) and/or CCTT1 and CCTT2 (patients only, 8 years and above). Information on school performance and familial educational background was assessed by questionnaire. School performance was rated as overall mark (German school marks 1=very good, 2=good, 3=satisfactory, 4=pass, 5=poor, 6=very poor). Results were compared to those of 296 healthy children (165f, median age 10 (2-18) years) using paired or unpaired t-test as appropriate. Healthy children were recruited from a primary and comprehensive school catering for all levels of secondary schooling (Gesamtschule). Correlation between test results and educational parameters was made using Pearson’s rho.

\textbf{Results:} Of 63 patients aged 10 years and older, basic level, mid-level and higher-level secondary education was achieved by 11.1%, 46% and 23.8%. This distribution is shifted towards lower educational levels compared to the general German population. Overall school performance was lower in patients compared to controls. Rates for good/satisfactory/pass/poor and very poor were 35.9%/41.5%/14.2%/2.8%/0% in the patients and 56%/17%/3.7%/0%/0% in the controls (p&LT; 0.01). In both patients and control children, results of the cognitive functioning measures CCTT2 and CogPedsQL correlated strongly with school performance (r = -0.32/-0.32/-0.32 and r = -0.2/-0.27/-0.57 for CCTT2/childrens CogPedsQl/parents in patients and controls respectively). While in control children both school performance and CogPedsQL scores correlated with parental education, in patients school performance of transplanted children correlated with the level of maternal primary education degree (r = -0.21, p = 0.03), but not with the education of their fathers (r = -0.11, p = 0.29). None of the patient CCTT or CogPedsQL test results correlated with parental school education.

\textbf{Conclusion:} Results of PedsQL\textsuperscript{TM} Cognitive Functioning Scale and CCTT1&2 in children after OLT reflect real life school performance. While overall school performance is reduced in transplanted children vs. healthy controls, they still achieve good educational results. The influence of parental education on school performance is reduced in transplanted children, which possibly indicates the overriding impact of transplant-associated morbidity on educational outcomes.

\textsuperscript{1}Childrens Colour Trail Test and PedsQL Cognitive Functioning Scale reveal impaired cognitive functioning in children after liver transplantation. I Goldschmidt, R van Dick, S Bockisch, ED Pfister, U Baumann, ESPGHAN 2014

\textbf{Disclosure of interest:} The study was supported by an unrestricted grant by Astellas Pharma

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Stability of cognitive functioning as tested by PedsQL\textsuperscript{TM} Cognitive Functioning Scale (CogPedsQL) and the Childrens’ Colour Trail Test (CCTT) depending on immunosuppressive regime

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**Background:** Previous analyses of the use of the PedsQL\textsuperscript{TM} Cognitive Functioning Scale (CogPedsQL) and the Childrens’ Colour Trail Test (CCTT) to assess cognitive functioning in children after liver revealed no difference in test results according to the immunosuppression (IS) taken at the time of the study\textsuperscript{1}. Data on the influence of any particular IS regime over time is still lacking.

**Aim:** To examine the influence of long-time calcineurin-inhibitor exposure on cognitive functioning as tested by CCTT and CogPedsQL, with a focus on longitudinal variations in test results.

**Methods:** 155 children (78f, median age 10.4 (1-18) years; 4.9 (0.1-17) years after OLT) underwent testing for cognitive functioning with either PedsQL\textsuperscript{TM} Cognitive Functioning Scale (child self-report and parent proxy-report) and/or CCTT1 and CCTT2 (patients only). Published normative data was used to interpret CCTT1&2. Follow-up tests were performed in 106 patients at a median of 0.57 years (range 0.2-3) after the first test. Results were compared using paired or unpaired ttest as appropriate. Correlation between test results and clinical parameters was made using Pearson’s rho.

**Results:** There was no difference in test results depending on whether children had received Tacrolimus or Cyclosporin as primary CNI, even when data was corrected for confounders such as length of exposure, age at transplantation or switch of primary CNI. If analysis was refined according to tacrolimus compound, patients on Cyclosporin had better CCTT2 results than patients on Prograf, while there was no significant difference in test results between children on Cyclosporine vs the slow-release formula Advagraf. Children who had ever experienced toxic levels of tacrolimus (≥ 20 ng/ml) tended to have lower test results, albeit without statistical significance (p=0.08). This trend was less pronounced for toxic levels of Cyclosporin (≥300 ng/ml).

Test results were stable over time with no significant changes between 1\textsuperscript{st} and 2\textsuperscript{nd} test from baseline to follow-up if the complete group was considered. Correlation of follow-up results with baseline results was highest for the parent proxy PedsQL (r=0.78, p<LT; 0.001). 25 patients were switched to Advagraf during the study period and underwent both pre- and post-switch testing. CCTT2 results improved after switch to Advagraf, albeit not significantly. Parent-proxy PedsQL results improved significantly from 57.4 ± 4.9 to 66.3 ± 4.9 (p=0.02). Post-switch testing was performed median 0.51 (range 0.37-1.9) yrs after switching the IS medication.

In comparison, in patients with stable immunosuppression throughout the study period, there was no significant change in CF measures. Delay between tests in this group was median 0.5 yrs (range 0.3-1.9).

**Conclusion:** Results of CCTT and CogPedsQL are stable over time in children after liver transplantation. While there appears to be no general advantage of Tacrolimus vs Cyclosporine or vice versa with regard to cognitive functioning, longitudinal measurements suggest an advantage of a slow-release formula for Tacrolimus.

\textsuperscript{1}Childrens Colour Trail Test and PedsQL Cognitive Functioning Scale reveal impaired cognitive functioning in children after liver transplantation. I Goldschmidt, R van Dick, S Bockisch, ED Pfister, U Baumann, ESPGHAN 2014

**Disclosure of interest:** This study was supported by an unrestricted grant by Astellas Pharma

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Roux loop revision for treatment of focal protein losing enteropathy in the Roux-Y loop after liver transplantation

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Objectives and Study: Protein losing enteropathy (PLE) is a rare complication following paediatric liver transplantation (LTx), mostly related to venous outflow obstruction of the liver. Here, we discuss diagnosing a thus far unknown cause of PLE following paediatric LTx and its surgical treatment.

Method: Case-study

Results: A boy received an LTx (segments 2 and 3, postmortal heart-beating donor, Roux-en-Y hepaticojejunostomy) at the age of 7 months because of ornithine transcarbamylase deficiency. At the age of 18 months, he developed generalized edema and ascites. PLE was diagnosed, as faecal alpha-1 antitrypsin levels were markedly increased. Clinically, he required suppletion of albumin intravenously every two weeks, for which a venous access port was implanted. Routine diagnostic work-up for PLE was negative. No infectious cause of PLE was found. Endoscopy (gastroduodenoscopy, capsule endoscopy) showed no mucosal injuries and no signs of lymphangiectasia. PET/CT scan showed no signs of post-transplant lymphoproliferative disorder. Vascular origin, most notably venous outflow obstruction, is a known cause of PLE following LTx. Therefore catheterisation was performed, which showed no signs of venous outflow obstruction (normal central venous pressure of 9 mm Hg in the inferior vena cava and normal pressure in the hepatic vein of 9 mmHg), and only a slightly increased wedge pressure in the hepatic vein (19 mmHg). A liver biopsy taken during the same procedure showed no relevant pathology. To find the localization of protein loss, an albumin scan (technetium-99m labeled albumin) was performed, which confirmed intestinal albumin loss. Of note, early recordings (dynamic 0-30 min and early static SPECT-CT recordings at 30, 60, 90 minutes after tracer injection instead of after 120 minutes) were done, to detect where albumin entered the intestine. The affected area on the albumin scan was where the Roux loop was expected. With regard to the albumin loss in the Roux loop, local bacterial overgrowth or local lymphangiectasia, possibly due to (venous) congestion, were considered. Treatment with Metronidazole did not improve albumin loss, rendering local bacterial overgrowth an unlikely cause of the PLE. Therefore a surgical revision of the Roux loop was performed. During the procedure, no torsion of the Roux loop was observed. The explanted loop macroscopically showed a small abnormal area with a thin hyperaemic mucosa (Figure 1A). Histological analysis showed focal lymphangiectasia (Figure 1B), which was considered the site of protein loss. Following surgical revision, PLE disappeared and serum albumin levels remained stable, up to now (6 months post-revision, Figure 1C). We suspect that the local PLE in the Roux loop arose from local congestion of lymphatic outflow.

Conclusion: Here, we report diagnosing a thus far unknown cause of PLE following LTx in a child. The Roux loop was found to be the site of albumin loss using early SPECT-CT recordings during an albumin scan. Notably, this was in the absence of relevant portal hypertension. Surgical revision of the Roux loop has stopped the PLE up to now, 6 months post-revision.
Figure 1:
A  Macroscopy of the resected roux-loop, with the abnormal area within the red square.
B  Histology of the area marked as abnormal in (A), with hematoxylin and eosin staining (left) and D2-40 immunohistochemistry (right) showing focal lymphangiectasia with dilated, sometimes anastomosing prominent lacteals and lymph vessels.
C  Change in faecal Alpha-1-antitrypsin (A1AT) and plasma Albumin following surgical revision of the Roux-loop.

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Is combined liver-kidney transplantation a good indication in autosomal recessive polycystic kidney disease?

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Objectives and Study: Autosomal Recessive Polycystic Kidney Disease (AR-PKD) is a ciliopathy caused by mutations in the PKHD1 gene. It is characterized by congenital liver fibrosis and cystic kidney disease. The objectives of this study were to describe the evolution of renal and hepatic function in children with AR-PKD and to discuss indications for renal or combined liver-kidney transplantation.

Method: We retrospectively analyzed clinico-biological data from 25 children with AR-PKD and followed at Necker Children's Hospital since 1985.

Results: In 24% of children, the diagnosis was suspected on prenatal ultrasonography. For the others, the median age at diagnosis was 1.8 ± 0.67 years. At diagnosis, 60% had isolated renal features, 8% liver features only, and 32% exhibited both liver and kidney features. Thirteen patients were &LT; 1 year old, and presented the same clinico-biological characteristics as the others, apart from more frequent arterial hypertension (p = 0.01). During the follow-up, hepatic features were mainly portal hypertension (64%, n = 16) with oesophageal varices in 48% (n = 12). Four patients presented with acute cholangitis, and only one experienced more than 3 episodes / year. None presented a chronic elevation of transaminases or hepatocellular insufficiency. At the last follow-up (FU) (mean FU of 11.1 ± 1.5 years), 8 patients (32%) had stage 1-2 chronic kidney disease (CKD) (mean FU of 6.7 ± 2.4 years), 7 had stage 3, and 4 had stage 4-5. Six children (24%) received a kidney transplant with a mean age at first transplantation of 9.3 ± 2.6 years. No synchronous or asynchronous combined transplantation was reported during childhood. However one 20 years-old patient received a preemptive combined liver-kidney transplantation due to repetitive cholangitis. Nineteen children (76%) were treated for high blood pressure at the last follow-up, or at the last pre-transplant consultation.

Conclusion: Liver survival in patients with AR-PKD is good in our cohort at least until adolescence. Combined liver-kidney transplantation seems to be very rarely indicated during childhood in this pathology. The evolution of children with early manifestations (&LT; 1 year) is similar apart from a higher frequency of arterial hypertension.
Is standard triple Immunosuppression effective in ABO incompatible pediatric living related liver transplants? Plasmapheresis versus immunoadsorption-what to choose?

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Objectives and Study: ABO-incompatible (ABOi) liver transplantation is usually contraindicated because of the risk of antibody-mediated humoral rejection of graft. Ours is a busy living related liver transplant (LDLT) center. We describe 6 successful cases of patients who had LDLT from ABOi donors.

Methods: Study period- January 2012 to December 2017. ABOi LDLT patients < 18 years of age. Protocol consisted of rituximab 2 weeks prior (in >3 years) and plasmapheresis before LDLT. Target anti ABO titres pre-transplant was less than 1:16. Plasmapheresis to aim anti-ABO titers below 1:32 was planned upto 4 weeks post-op. Mycophenolate was started one week prior to transplant. No child was splenectomized and no local graft infusion used. Standard triple immune suppression (Steroid, Mycophenolate Mofetil and Tacrolimus) was used post operatively.

Results: Out of 160 Pediatric LDLT patients, 6 were ABO incompatible (ABOi). Indications- Biliary Atresia- 4; PFIC - 2. Median age 28.5 months (7-91); median PELD score 24 (19-42). Mean graft-to-recipient weight ratio 1.85. Initial range of isoagglutinin IgM and IgG titers were 1:32-1:256 and 1:64-1:256 respectively in 5 patients on whom 2-6 cycles of plasmapheresis done preoperatively. One patient had titre 1:1024 where Glycosorb immuno adsorption technique was used in view of 3 failed plasmapheresis, along with Rituximab. The same cassette of Glycosorb was reused thrice to bring down titre (1024 - 256 - 128 - 8). Post operative IVIG and plasmapheresis was used in 2 patients each. No rejection, bacterial or fungal infections noted. Postoperative complications included portal vein thrombosis in one, successfully reanastomosed and CMV infection one. Mean hospital stay was 23.4 days (18-23). Patient and graft survival was 100% at a mean follow-up of 33 months (2- 71 months).

Conclusions: ABO-incompatible LDLT can be safely performed with excellent outcome using standard immuno-suppression by preoperative reduction of antibody titres &LT; 1:16. Immuno-adsorption technique is more effective than routine plasmapheresis with very high antibody titres preoperatively. Glycosorb could be reused thrice with good efficacy.

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**Objectives and Study:** Liver transplantation (LT) has evolved as a promising therapeutic approach for a growing number of metabolic diseases. The transplanted liver provides sufficient enzymatic activity to correct, at least in part, the genetic defect. Therefore, no longer simply life-saving, LT can improve prognosis and quality of life by removing/reducing the risk of metabolic decompensation and the need for dietary restrictions. We evaluated impact of LT in a large cohort of children with inborn errors of protein metabolism.

**Methods:** This is a retrospective analysis on 24 patients with different inborn errors of protein metabolism, undergoing LT from 2008 to date at Bambino Gesù Children's Hospital: 7 with urea cycle defects [(UCDs), 4 ASL, 2 OTC, and 1 with CPS deficiency]; 5 with hepatocellular carcinoma and 1 with chronic liver failure (with previous hepatoblastoma) in tyrosinemia type 1 (TYR1), 5 with MSUD, 4 with methylmalonic (MMA) and 2 with propionic aciduria (PA). The mean age at NTBC start in Tyr 1 patients was 18.5 months (range 5-39).

**Results:** Patient and graft survival was 100% and all children had normal graft function after a mean follow up of 30±25 months. Protein tolerance normalized after LT and natural protein intake by diet reached the RDA for age in all patients in a mean time of 2.8 months (range 1-5 months).

<table>
<thead>
<tr>
<th></th>
<th>UCD (range) months</th>
<th>MSUD (range) months</th>
<th>TYR 1 (range) months</th>
<th>PA/MMA (range) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at LT</td>
<td>27.5 (12-76)</td>
<td>17 (7-74)</td>
<td>48 (1-62)</td>
<td>8.5 (2-49)</td>
</tr>
<tr>
<td>Mean natural protein intake (g/kg/day) before LT</td>
<td>0.65±0.12</td>
<td>0.42±0.08</td>
<td>0.74±0.16</td>
<td>0.9±0.05</td>
</tr>
<tr>
<td>Mean natural protein intake (g/kg/day) after LT</td>
<td>1.75±0.27</td>
<td>1.28±0.11</td>
<td>1.15±0.36</td>
<td>1.58±0.10</td>
</tr>
</tbody>
</table>

[Protein intake before and after LT]

In MSUD leucine tolerance increased more than 5-fold (452±17 vs 2329±386 mg/kg/day, p=0.001), reaching the RDA for age in all patients after a mean time of 4 months after LT (range 2-8). As far as concerns primary offending compounds, these are the results recorded before and after LT. In ASL deficiency, plasma levels of argininosuccinic acid decreased by 445±45 to 112±7 µmol/L (p< 0.001). In MSUD, branched-chain amino acid levels were corrected within two days after surgery and remained stable during the follow-up: plasma leucine (265±32 vs 206±7, p=0.009) and alloisoleucine (136±12 vs 15±1.5; p= 0.0001) significantly decreased after LT. In MMA, plasma MMA levels significantly reduced after LT (606±414 vs 206±180, p< 0.0001). Similarly, levels of tyrosine in TYR 1 resulted markedly reduced after LT (437±35 vs 190±43, p=0.0005). At follow-up all TYR1 patients interrupted NTBC therapy and their plasma succinylacetone was undetectable but was detectable in traces in urine.

**Conclusion:** Although avoidance from metabolic crisis and progression of brain injury could not be
fully prevented, LT is an effective long-term treatment for protein/aminoacid-related inherited disorders. Protein tolerance is an achievable goal in all patients. At the same time, biochemical parameters indicate that LT allows a significant improvement of metabolic profiles along with clear improvement of disease course and quality of life. Furthermore, specific therapy may be safely suspended, with the exception of carnitine in organic aciduria. The relatively high rate of HCC in TYR 1, not prevented by late initiation of NTBC therapy, highlight the need of an early diagnosis by including TYR in the disease panel screened at birth.

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Passenger lymphocyte syndrome in paediatric liver transplant

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Objectives and Study: Passenger lymphocyte syndrome (PLS) is an acute immune-mediated haemolytic anaemia seen in recipients of compatible non-identical ABO (niABO) organ transplants. It is often mild and self-limiting but may require blood transfusions (PRBC) +/- steroids, plasmapheresis or anti-CD20 monoclonal antibodies. To date, PLS after paediatric liver transplant (LT) has only been reported as the occasional subject within adult series. This single-center retrospective study aimed i) to determine the prevalence and clinical course of PLS in recipients of paediatric compatible niABO LT and ii) to determine risk factors for the development of PLS.

Method: Patient inclusion criteria included all recipients < 18 years at time of niABO isolated LT between Jan 2000 and Aug 2017. Excluded were multi-organ transplants. Recipient demographics, donor and organ information, and 30 day post-operative course were reviewed. PLS was diagnosed by a drop in haemoglobin with a positive DAT and one other laboratory finding of haemolysis. Chi square tests were used to compare categorical variables and student’s t-tests were used for continuous variables between those with and without PLS.

Results: Amongst a total of 267 paediatric LT recipients, 40 (15%) received niABO (O into A: n =22, O into B: n=10, A or B into AB: n=8) grafts. PLS was diagnosed in 6 (15%; all A+ receiving O+ graft) recipients (4 biliary atresia, 1 Alagille and 1 fulminant hepatic failure (FHF)). Although patients with PLS were younger (2 vs. 4.1y), no statistically significant differences in primary diagnosis, gender, viral status, graft type (living vs. deceased) or immunosuppressant (IS) therapy were identified with those who did not develop PLS. There was a median reduction in haemoglobin of 35.5 (range 16-43) mg/dL at median 10 (range 8-13) days post LT. DAT was positive in 6/6, elevated reticulocyte count 6/6, unconjugated bilirubin 4/6, LDH 3/6, decreased haptoglobin 1/6 and anti-A antibody detected in patient eluate 4/6. A second acute drop in haemoglobin (mean 27, range 20-41 mg/dL) occurred in 5/6 patients at median 3 days after first event. All 6 had documented fever median 2 days before the first haemolytic episode. Haematology consultation was obtained in 5/6 patients. All patients received blood transfusions (median 2). Two patients initially received recipient blood group PRBCs. In one, haemolysis resolved despite 2 transfusions with only recipient group A PRBC. The other patient was subsequently transfused with donor PRBC. This patient was the only FHF in this series, required 5 transfusions during the first 30 days post LT and had recurrence of primary disease progressing to multi-organ failure outside the study period. In the other 5/6 patients, haemolysis resolved at median 15 days post LT. 0/6 required change in IS, plasmapheresis or anti-CD20 monoclonal antibody.

Conclusion: PLS occurred in 15% of children receiving a niABO LT. Risk factors include use of O+ grafts in A+ recipients, and younger age at LT. Early diagnosis and blood transfusion with donor compatible PRBC can avoid unnecessary transfusions. PLS is an important aetiology for unexpected and early acute anaemia in paediatric niABO LT.

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MicroRNA-17, MicroRNA-19b, MicroRNA-146a, MicroRNA-302d expressions in hepatoblastoma and clinical importance

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Objectives and Study: Hepatoblastoma (HB) is the most common primary liver malignancy in children, usually occurring in the first 3 years of life. The pure fetal-type HB has the best prognosis, whereas the small cell histology has been associated with unfavorable outcome. In the present study, we aimed to characterize the expression level of selected microRNAs (miRNAs) in HB subtypes, and to consider the association with the prognosis.

Method: A total of 22 Formalin fixed paraffin embedded (FFPE) HB tumor samples were evaluated in this study. Total RNA was isolated from frozen tissue sections and areas of tumor. Expressions of miR-17, miR-146a, miR-302d, and miR-19b were analyzed in 22 HB cases by qRT-PCR. To make the relative quantitation of the results, ΔΔCt method was used. MiRNA Ct values were normalized by Snord 48 housekeeping gene with this method. Comparative 2-ΔΔCt methods were used for the cycles above threshold values.

Results: The patient group included 22 children (mean age months, 38,14 range 3-204) diagnosed with HB. Lower miRNA-17 expression levels were obtained in tumor samples in comparison with non-tumorous surrounding liver samples (p=0,028). Lower miRNA-17 expression was significant for predicting prognosis in HB patients (AUC=0,875, p=0.044). A higher-level of miR-19b was found in embryonal samples (p=0.008). Overall and event free survival were not found correlated with miRNA expressions in both embryonal and fetal subtypes (p>0.05).

Conclusion: In conclusion, it is thought that miRNA-17 and miRNA-19b in the miRNA-17-92 cluster can provide important data on diagnosis and prognosis in HB patients who show different clinical behaviours.
Effects of activation of the Liver X Receptor (LXR) in conditions of unconjugated hyperbilirubinemia

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Objectives and Study: Unconjugated bilirubin (UCB) can accumulate in neonates and in patients with Crigler-Najjar disease. We previously demonstrated that transintestinal secretion of UCB is a major route of disposal in the Gunn rats, an animal model for Crigler Najjar disease. A transintestinal pathway has also been identified for cholesterol, which could be stimulated by activation of the transcription factor LXR and by the cholesterol absorption inhibitor ezetimibe. It is not known whether these two strategies also affect the transintestinal secretion of UCB. We determined the effects of LXR activation, of ezetimibe, and of the combination of these, on UCB elimination in Gunn rats.

Method: We performed a short term study in adult male Gunn rats: one dose of T09 (80 mg/kg) by oral gavage and sacrificed them two days later. We also extended treatment duration: for 14 days, Gunn rats received standard chow or chow containing either the LXR agonist T09 (20 mg/kg/day), ezetimibe (0.005% w/w), or a combination of these compounds.

Results: A single dose of T09 decreased total serum bilirubin (TSB) in Gunn rats by 40% within two days. T09 administration for 2 weeks, however, increased serum TSB levels, by +132% (P=0.003). T09 treatment for 2 weeks decreased body weight (-5%, p=0.047), but increased liver weights (+72%, relative to body weight, p<0.001) Neither ezetimibe alone nor the combination of ezetimibe and T09 altered serum TSB levels or liver weights of Gunn rats, compared to control diet.

Conclusion: Short-term activation of LXR decreased TSB in Gunn rats, but prolongation of the treatment increased serum bilirubin concentrations. Our data suggest that activation of LXR can affect UCB metabolism at different levels and is not uniformly applicable to treat unconjugated hyperbilirubinemia. Finally, our data strongly indicate that the transintestinal secretion pathways for cholesterol and for bilirubin are distinctly regulated.


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Native liver survival in paediatric patients with cirrhosis and large, recurrent, diuretic-resistant ascites

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Objectives and Study: Ascites that does not respond or recurs after high-dose of diuretics and sodium restriction is a poor prognostic sign, well recognised in adults with cirrhosis. Large-volume paracentesis (LVP) associated with albumin infusion is the initial treatment for this condition. To the best of our knowledge, there are no published data on patients with large, recurrent, diuretic-resistant ascites in children. We aimed to analyse the native liver survival in children with ascites diuretic-resistant underwent to large-volume paracentesis (LVP).

Method: Clinical, demographic and biochemical data were retrospectively and prospectively analysed from a cohort of children with cirrhosis (age ≤ 18 years) and ascites grade 3 with no satisfactory response to diuretics and sodium restriction, underwent to LVP (removal of volume ≥ 50 mL/Kg of dry body weight). Native liver survival was defined as patient survival without liver transplantation. Survival analysis was carried out by Kaplan-Meier method.

Results: We performed 96 LVP sessions in 38 patients median age=0.7y (1 month -17.45 y) who presented from December 2005 to September 2017 at our institution. Biliary atresia was the most prevalent diagnosis (55.2%), 34 patients were classified as Child-Pugh C at the time of the first LVP, and PELD scores ranged from -3 to 70. The INR ranged from 0.84 to 13.4 (median 2: p25=1.5; p75=2.9). The median of platelets count was 99.500 (p25=63300; p75=144500). The LVP was performed under conscious intravenous sedation in 66 sessions. Vital signs and oxygen saturation were continuously monitored. Most patients received albumin infusion (human albumin 20% - median dose 0.76g/kg). The number of LVP sessions per patient ranged from 1 (50%) to 17 (2.6%). The volume removed ranged from 140 mL to 6.9 liters (median 672 ml p25=485 mL - p75=878mL) equivalent to a median = 83.9ml/kg (p25: 66.7 - p75: 116). The main complication observed was hypotension (6.2%). Thirty-three patients (86.8%) lost their native liver (33.3% underwent liver transplantation, and 66.6% died). The gap between LVP and transplantation or death ranged from 2 days to 2.5 years. In 60 days after the procedure, 60% of the patients lost their liver. Five patients are alive with their native liver (follow-up after LVP = 1.5 - 7.1 years).

Conclusion: Ascites diuretics-resistant was associated with a decrease in native liver survival in children.

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Alagille syndrome: a new mutation of JAG1

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Background: Alagille syndrome (ALGS; OMIM 118450) is an autosomal dominant disorder that results from defects in the Notch signaling pathway, typically mutations in the gene encoding a ligand for Notch receptors, JAG1. It is one of the causes of pediatric chronic liver disease and occurs with a frequency of 1 in 70,000 newborn infants. ALGS is associated with a wide variety of clinical features and manifestations, including abnormalities of the liver, heart, skeleton, eyes, kidneys, and facial features. JAG1 mutations and/or ALGS clinical features have been reported in various populations, such as American, European, Australian, and Japanese. Nearly 500 JAG1 mutations have been identified (HGMD Professional 2015.1). The majority (90-94%) of ALGS cases are caused by mutations in the JAG1 gene, and in a small percent of patients (1-2%) mutations in the NOTCH2 gene or deletions in 20p12 region in 7% of patients have been described. The diagnosis is based on clinical features and liver biopsy typically shows paucity of the intrahepatic bile ducts, but it is no longer considered mandatory to make a diagnosis of ALGS, and the presence of cholestasis is acceptable to fulfill this criterion. Confirm of diagnosis is molecular by genetic mutation. We describe a patient with Alagille syndrome with a previously underscribed mutation in the JAG1 gene of the exon number 22.

Case presentation: Our patient was a male, 9 month old. His height was 78 cm (z-score < 3), weight 6.8 kg (z-score < 3), and head circumference < 3. He had mild pallor, clubbing, and scratch marks over his skin. Our patient had peculiar facial features. The biochemical parameters show triple values of AST, ALT, GGT, normal metabolic and infection parameters. Because of systolic heart murmur, an echocardiography was necessary and it showed pulmonary stenosis of moderate degree. Eye examination shows papilledema. Ultrasound examination of liver was normal. Butterfly vertebrae at D5 as seen in X-ray was one of the most important characteristic. Karyotype and CGH array were normal. Molecular analysis of the gene JAG1: heterozygous mutation in in the exon number 22.

Child was started on ursodeoxycholic acid, after which itching decreased.

Discussion and conclusions: Jag 1 is involved in the Notch signaling pathway. The JAG1 gene encodes a cell surface ligand, whereas the NOTCH2 gene encodes one of the four human Notch receptors. The JAG1 gene is located within chromosome 20p12 and contains 26 exons encoding a conserved transmembrane protein. The JAG1 protein contains several evolutionarily conserved. Over 440 various JAG1 mutations have already been described in ALGS patients. The most common are frameshift mutations (49%), nonsense mutations (16%), missense mutations (15%), gross deletions and insertions (11%), while the least frequent variants are splice site mutations (9%). Molecular analysis identifies point mutation in heterozygous, in exon number 22 and reveals a deletion c.2606-2607 del TG consistent in a premature termination codon (p.Val86Asp*)9, probably related with early hepatic onset with characteristic face and failure to thrive. To conclude, this mutation has not been reported in other ALGS patients and has also not been reported as a normal variation which predicted to be probably damaging to the protein function.

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Clinical presentation and long-term outcomes of type 1 tyrosinemia in Finland

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Objectives and Study: While type 1 tyrosinemia is globally rare, it has enriched in certain geographical areas for example in Northern Europe and Canada. Liver transplantation used to be the only cure, but discovery of nitisinone medication has revolutionized the treatment. In addition, recently launched newborn screening programs should reduce the diagnostic delay. However, effects of these changes on the presentation and long-term outcomes of tyrosinemia are scarcely studied. We investigated the clinical presentation and long-term treatment outcomes of type 1 tyrosinemia in Finland.

Methods: All known tyrosinemia patients monitored in our hospital were included. In addition, to detect possible earlier cases, the medical records of all children (n >2000) with a diagnosis code indicating metabolic disease or liver failure were screened from the year 1980 onwards. The data collected from confirmed patients included clinical presentation and laboratory and radiology findings at diagnosis, implementation of liver transplantation or nitisinone treatment and long-term treatment outcomes.

Results: Tyrosinemia was diagnosed in 18 patients of whom 17 were currently alive. Median age at diagnosis was 1.7 months and 10 (56%) were girls. Sixteen (89%) patients had Northern European type W262X mutation. Four (22%) patients were found by screening; three by newborn screening and one due to siblings’ tyrosinemia. The most common diagnostic findings were liver failure (82%), hypoglycemia (50%), unexplained fever (44%), ascites (40%), rickets (40%) and growth delay (40%). One patient had kidney failure and one transient cardiac dysfunction. Also, two screen-detected patients had incipient liver failure. Imaging studies revealed liver abnormalities in 73%, bilateral renal enlargement in 53% and splenomegaly in 27%. The mean levels of plasma tyrosine and alpha-fetoprotein (AFP) were 623 µmol/l and 192200 kU/l, respectively. Median nitisinone starting dose was 1 mg/kg/day. Six patients received a liver transplant before introduction of nitisinone and two late-diagnosed patients in nitisinone era due to premalignant changes. Median follow-up time after the diagnosis was 13.6 (range 0.5-29.7) years. After one year on treatment the mean plasma levels of nitisinone, tyrosine and AFP were 58.4 µmol/l, 679.2 µmol/l and 32 kU/l, respectively. There were no significant differences in AFP or tyrosine levels at diagnosis, after one year on treatment or in the end of follow-up between screen- and clinically-detected patients. The most common complications during later follow-up were osteopenia/osteoporosis (n=6), growth disturbance (n=2), developmental delay (n=2) and kidney tubular dysfunction (n=2). Furthermore, three transplantation patients needed a new liver transplant.

Conclusions: Although even screen-detected patients may still have significant clinical symptoms and findings at diagnosis, the prognosis of type 1 tyrosinemia is nowadays generally good and severe long-term complications rare. Newborn screening programs are important to reduce morbidity and the risk of complications caused by delayed diagnosis.
Clinical and molecular genetic features of early childhood Cerebrotendinous Xanthomatosis, in Saudia Arabia

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Objectives: Cerebrotendinous xanthomatosis (CTX) is a rare inherited disease. It is a result of bile acid synthetic disorder secondary to mutations in the cytochrome P450 CYP27A1 gene. Estimated prevalence is about 1/50,000 among Caucasians. It is characterized by cataract, tendon xanthomata, and neurologic dysfunction. It usually presents with neonatal cholestasis or and infantile diarrhea, however 75% of CTX cases were diagnosed late, following development of cataract and neurological dysfunction later in life. The neonatal and early childhood cases of CTX are usually detected upon genetic screening. Herein we report two siblings who diagnosed with this rare condition in early infancy.

Method/ Patients: Two sibling presented with intractable diarrhea were studied for disease history, genetic mutation in CYP27A1 and the response to therapy.

Results: Two siblings (a male and a female 3.5 years and 9 months respectively had intractable diarrhea, failure to thrive and cholestasis. The eldest patient presented with neonatal cholestasis, with a later development of intractable diarrhea.Extensive laboratory work up for intractable diarrhea and cholestasis were done, The test for urine bile acids mass spectrometry came suggestive of CTX. The diagnosis was confirmed by detection of homozygous mutation in CYP27A(g.219677818C>T;NM_000784.3:c.1016C>T(p.(Thr339Met)). The patient responded to chenodexycholic therapy. His sister presented with intractable diarrhea and failure to thrive without neonatal cholestasis, and found to have the same disease upon genetic testing. She responded to the same medication as well.

Conclusions: CTX should be considered in differential diagnosis of neonatal cholestasis, and intractable diarrhea of infancy. With a high rate of consanguinity in our community, we think that this disease is under diagnosed. Early diagnosis will prevent the subsequent neurological disability later in life. To the best of our knowledge these are the first reported cases in Saudia Arabia.

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Protective effects of tribulus terrestris, ashwagandha and N-acetylcysteine on liver fibrosis in carbon tetrachloride induced rats

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Objectives and Study: Fibrosis, a process of chronic liver disease, can be prevented before the development of cirrhosis when it is diagnosed and treated early. In this study, the effects of Tribulus terrestris, Ashwagandha and N-acetylcysteine were investigated in an experimental model of liver fibrosis induced by carbon tetrachloride (CCl₄).

Method: Fifty Wistar rats were divided into five groups of 10 each as follows: 1) Control group, 2) CCl₄, 3) CCl₄ plus N-acetylcysteine, 4) CCl₄ plus Tribulus terrestris, 5) CCl₄ plus Ashwagandha administered groups. At the end of six weeks, rats were sacrificed and serum and tissue samples were collected. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), malondialdehyde (MDA), nuclear factor kappa B (NF-κB), collagen 1, nuclear factor erythroid-2-related factor 2 (Nrf2), tumor necrosis factor-α (TNF-α); hepatic steatosis score, necrosis, inflammation and fibrosis levels were analyzed.

Results: There was no significant difference between the group treated with N-acetylcysteine and the other two groups treated with Tribulus terrestris and Ashwagandha in serum ALT and AST levels (p>0.05). GGT levels were decreased in rats treated with N-acetylcysteine compared with the other two groups which were treated with Tribulus terrestris and Ashwagandha (p<LT; 0.001). Liver MDA levels were lower in the N-acetylcystein, Tribulus terrestris and Ashwagandha treated groups than in the CCl₄-administered group (p<LT; 0.001). There were differences between the groups in terms of NF-kB, collagen 1, Nrf2 and TNF-α levels (p<LT; 0.05). Histopathologically, the rates of fibrosis reversal were evaluated as close to each other in both plant extracts.

Conclusion: Tribulus terrestris, Ashwagandha and N-acetylcysteine were found to have protective effects on the liver in the experimental fibrosis model.
Cholestasis and glutaric acidemia Type II: A case report

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Objectives and Study: To describe the clinical presentation, laboratory findings and outcome of a patient with Glutaric Acidemia type II.

Method: A case report of a patient with Glutaric Acidemia type II who received care at the National Institute of Pediatrics in Mexico City.

Results: A 1-month-old male was admitted because of jaundice since 2 days of life. Parents denied acholia or choluria during this time. He had a history of prematurity of 36 weeks, neonatal sepsis and blood transfusions. Upon physical examination, the patient showed generalized jaundice and facial abnormalities (high forehead, flat nasal bridge and telecanthus). A systolic cardiac murmur was heard. The rest of examination was normal. Hepatic ultrasound, TORCH tests and alpha-1 antitrypsin were within normal limits. Initial liver enzymes and liver function tests are shown in Table 1.


<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>335 UI/L</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>370 UI/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>342 UI/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>326 UI/L</td>
</tr>
<tr>
<td>Gamma glutamyl transferase</td>
<td>99 UI/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.1 mg/dl</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>13.9 sec</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>32.7 sec</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>13.1 mg/dl</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>3.9 mg/dl</td>
</tr>
</tbody>
</table>

[Table 1. Shows initial liver enzymes and liver function tests]

During hospitalization, he developed multiple episodes of hypoglycemia and metabolic acidosis. A metabolic disorder was suspected, and an expanded newborn screening was obtained, which was consistent with Glutaric Acidemia type II. Echocardiography showed the presence of patent ductus arteriosus and atrial septal defect. Auditory and visual assessments showed the presence of visual alteration in both aferences and severe bilateral hearing loss with left predominance. The patient was managed with a high-carbohydrate, fat and protein restriction diet, liposoluble vitamins, vitamin C, ursodesoxicolic acid (30mg/kg/dia), riboflavin, coenzyme Q-10 and L-carnitine. Given the presence of Down syndrome-like facies, a karyotype was performed (pending results). The patient has been stable since discharge.

Conclusion: Glutaric Acidemia type II is an autosomal recessive inherited disorder of fatty acid, amino acid, and choline metabolism. It is a clinically heterogeneous disorder ranging from a severe neonatal presentation with metabolic acidosis, cardiomyopathy and liver disease, to a mild childhood/adult disease with episodic metabolic decompensation, muscle weakness, and respiratory failure. Birth prevalence is estimated at 1/200,000 but great variation is seen between countries/ethnicities. It is uncommon for this disorder to present with jaundice. Most patients present with metabolic acidosis, hypoglycaemia and congenital anomalies as in the case of our patient. It is important to perform extensive screening on a patient with cholestasis in order to diagnose, initiate prompt treatment and avoid complications. Treatment for the more severe phenotypes involves restriction of both fat and protein and reliance on a high carbohydrate diet. Strict avoidance of fasting and of other precipitating factors is necessary.
stresses is essential. Riboflavin supplementation is a very effective treatment for patients with Glutaric Acidemia type II as is CoQ10 supplementation in some.

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Objectives and Study: An 11 year old Saudi girl was referred to our hospital with jaundice, calicular cholecystitis, coagulopathy, and history of severe recurrent hypocalcemic tetany, first encountered at the age of 8 months old. There was history of transient jaundice at birth, resolved by 6 weeks of age. At our hospital, in May 2016, she had jaundice, no pruritus, and she had failure to thrive. There were no dysmorphic features, and the clinical examination was otherwise unremarkable. At presentation she had ALT 107.6 U/L, AST 171.3 U/L, ALP 288.6 U/L, GGT 96 U/L, total bilirubin 58.8 umol/L, bile acid 51.5 umol/L, PT 20 seconds, PTT 46.7 seconds, INR 1.7, vitamin D 23 nmol/L, vitamin A 99 ug/L, vitamin E < 2.2 mg/L, WBC 6.02 x 10^9/L, hemoglobin 122 g/L, platelet count 142 x 10^9/L, sickle cell negative, G6PD normal, antinuclear antibody negative, autoimmune markers negative, immunoglobulins unremarkable, viral serology unremarkable, TORCH screen negative. Routine dysmorphic survey showed mild generalized osteopenia, a few gallstones, no evidence of significant bony dysplastic changes or anomalies. Ultrasound abdomen showed a mild increase in the liver parenchymal echogenicity with no focal lesion and a normal duplex scan of the hepatic vessels. Her liver biopsy in showed extensive septal fibrosis and early cirrhotic transformation. The portal tracts showed mild focal chronic inflammatory cell infiltrate with significant fibrosis. All the portal tracts contained adequate bile duct branches and showed minimal ductular reaction. The periportal hepatocytes showed cytoplasmic ballooning with excess deposition of copper associated protein. Immunohistochemistry revealed cytokeratin 19 staining of bile ducts with few reactive cholangiocytes. The picture was of end-stage biliary cirrhosis, consistent with probable familial cholestasis. The patient was kept on ursodeoxycholic acid 250 mg oral twice daily, activated Vitamin D 0.5 mcg oral daily, vitamin K 5 mg oral daily, vitamin E 400 units oral daily, multivitamins with minerals 1 tablet oral daily.

Her latest lab results were ALT 30.7 U/L, AST 39.7 U/L, ALP 445.1 U/L, GGT 30 U/L, Alb 48.3 g/L, bilirubin 25.8 umol/L, bile acid 17.4 umol/L, AFP 2 ug/L, PT 14.6 seconds, INR 1.1, PTT 38.3 seconds, urea 2.5 mmol/L, creatinine 32 umol/L, and Ca 2.01 mmol/L.

Methods: Next generation sequencing (NGS), gene panel analysis, was sent in October 2016. Genomic DNA from leukocytes of this individual was used to build a PCR library of the coding sequence. The NGS resulted in >95% coverage of the targeted regions. Filtered variants were then further curated by expert opinions and reported based upon guidelines of the American College of Medical Genetics for sequence variants.

Results: The NGS showed a homozygous loss of function variant of HSD3B7 (HSD3B7:NM_025193:exon6:c.694+2T>-), a likely pathogenic mutation involved in congenital bile acid synthesis defect type 1, autosomal recessive.

Conclusion: Our patient was investigated for cholestasis, failure to thrive, and early severe vitamin D deficiency. The common causes of cholestasis were excluded, and the NGS was requested. We identified a novel HSD3B7 gene mutation in our patient, which could be a new underlying pathogenesis of 3β-HSD deficiency.
[Serum bile acids in 2016 - 2017]

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Evaluation of body fat mass and fatty liver in obese children

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Objectives and Study: To compare the bioelectric impedance analysis (BIA) with indirect measurement methods in the evaluation of body fat mass and to determine the diagnostic value of BIA in the diagnosis of fatty liver and metabolic syndrome (MS) in obese children.

Method: One hundred and fifty obese children were prospectively reviewed. All patients were evaluated by BIA and indirect measurement methods. Blood biochemical parameters such as glucose, lipids and insulin levels were studied and oral glucose tolerance test was performed. Fatty liver was assessed by ultrasonography. Metabolic syndrome was diagnosed according to the International Diabetes Federation criteria.

Results: The study included 150 children (females/males: 85/65, 12.9±2.7 years). MS was diagnosed in 58 patients. Fatty liver was detected in 101 patients. There were no gender difference in terms of fatty liver and MS. Fatty liver was found in 93% of patients with MS versus 51% of those without MS. Body mass index (BMI), upper mid-arm circumference, waist circumference (WC), and hip circumference values were significantly increased in patients with fatty liver, but there was a stronger correlation between fat mass (FM) and fatty liver compared to indirect measurement methods. FM was more significantly correlated with the diagnosis of metabolic syndrome than WC.

Conclusion: With the need for comprehensive and supportive studies, the measurement of body fat mass by BIA can be used together with the indirect measurement methods to detect the fatty liver and it may be an alternative diagnostic criterion instead of waist circumference measurement for diagnosis of MS in children.

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Clinical features, laboratory findings and prognosis in fulminant Wilson’s disease

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Objectives and Study: We evaluated our 16 years of experience of pediatric patients with fulminant Wilson’s disease.

Methods: Out of 98 pediatric patients with fulminant liver failure, 12 (12.2%) had fulminant Wilson disease. We reviewed the clinical and laboratory data of patients with fulminant Wilson’s disease. The patients’ PELD-MELD, Child-Pugh scores and new Wilson indexes at the time of application were calculated. The prognosis of the patients were also recorded.

Results: There were a total of 12 fulminant WD patients, 9 of them were female (75%). The mean age at the time of arrival was 9.3±1.59 years (min-max: 7.3-12.5 years). Four patients did not have any findings of encephalopathy, while 2 patients had stage 1, 3 had stage 2 and 3 had stage 3 encephalopathy at the time of admission. Six patients had ascites.

The mean hemoglobin, white blood cell count and thrombocyte levels were 7.43±2.67 g/dL, 20 330±12 430/mm³ and 131 820±93 650/mm³, respectively. The liver function tests at the time of reference were as follows: total bilirubin: 39.26±15.66 mg/dL, direct bilirubin: 27±11.76 mg/dL, AST: 513.66±943.6 U/L, ALT: 164.6±331.8 U/L, GGT: 78.4±71.8 U/L, ALP: 234±250.6 U/L, albumin 2.8±0.73 g/dL, prothrombin time 36.44±16.29 sec, INR 4±2.25. The mean creatinine value was 0.83±0.24 mg/dL, the mean glomerular filtration rate was 77.66±64.84 ml/min/1.73 m² and five patients were recorded to have tubulopathy during follow up. Nine patients had low seruloplasmin levels. The seruloplasmin levels varied between 5.9-26 mg/dL, with a mean level of 13.8±7.4 mg/dL. The 24-hour urine copper could be measured in 4 patients and the mean level was 430±600 µgr/dL. The challenge test could be performed in another 4 patients and the mean urine copper was 3155±2490 µgr/dL.

The mean PELD values, Child Pugh scores and new Wilson indexes were 32,1±11.5 (min-max: 16-48), 11.44±1.66 (min-max: 10-15) and 15.44±1.94 (min-max: 12-18), respectively. There was only one patient above 11 year of age with a MELD value of 40.

Plasmapheresis was used in all patients, while D-penicillamine were also given in three patients, D-penicillamine, zinc and steroids to two; trientine, zinc and steroids to two patients. Four patients died, six underwent liver transplantation and two patients spontaneously survived.

The histopathologic examinations of explant livers or postmortem liver necropsy samples were evaluated in 9 patients. Seven patients had cirrhosis, one had findings of chronic active hepatitis and the other one had diffuse microvesicular steatosis. The mean tissue copper level was 440±347 µgr/g dry liver tissue.

Five patients who underwent liver transplantation had living related donors. One patient had cadaveric donor. These patients were followed up for 9±3.3 years (min-max: 4.5-12 years) after transplantation.

Conclusions: Fulminant Wilson’s disease is extremely fatal if liver transplantation cannot be performed. Introduction of plasmapheresis and chelating therapy may be life-saving in low risk patients. Most patients have findings of cirrhosis on liver histopathological examination at the time of arrival.
HEPATOLOGY - General Hepatology

H-P-013

Aetiology and outcome of Acute liver failure in children in the United Arab Emirates (UAE)

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Introduction: Paediatric Acute liver failure (ALF) is characterized by severely impaired liver function, with or without encephalopathy in children without previous liver disease. Geographic location affects aetiology, with Non-A-E hepatitis and drugs accounting for the majority of cases in the west.

Objectives and Study: We aim to review the aetiology, presentation and outcome of ALF in children in the UAE.

Method: This is a retrospective, single centre study of children presenting with ALF from birth to 16 years over a 7-year period (September 2010-2017). We used the Paediatric ALF Study Group criteria for defining ALF: 1) absence of a previously known history of chronic liver disease, 2) biochemical evidence of acute liver injury, and 3) hepatic-based coagulopathy defined as PT≥15 s or INR≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or PT≥20 s or INR≥2 regardless of the presence or absence of clinical HE.

Results: 81 patients were identified (48 males and 33 females). Median age at presentation was 18 months (range 2 days-16 years). 12% presented in the first 4 weeks of life and 88% between 1-16 years of age. The aetiology was identified in 86% and included; 49% infection, 16% metabolic (The main cause of metabolic disease was Wolcott Rallison syndrome, seen in 46%), 15% acute circulatory failure, 14% indeterminate, 4% toxic and drugs, 1% infiltrative disease and 1% autoimmune hepatitis. Jaundice was seen in 42% at presentation (Median bilirubin 43 (range 2.2-600)) and didn't favour any aetiology. Encephalopathy was more significantly seen in the metabolic disease (77%, P=0.013). Renal failure was seen more significantly in acute circulatory failure (83%, P=0.008). INR was highest in toxic group (Median 6.5 (range 2.7-7.2)) and infiltrative disease (INR >10). Highest AST was in Indeterminate (Median 1059 (range 116-1435)) and Metabolic groups (Median 947 (range 38-9515)). Ammonia levels were highest in urea cycle defect (Median 455 (range 264-646)). Overall survival was 57% with improved survival in patients presenting after 1 month of age (68%). Only three patients were transplanted and they all survived. Metabolic, toxic and autoimmune disease had most favourable outcome with 60%, 100% and 100% survival respectively.

Conclusion: ALF in the UAE has unique aetiology; with increased number of infections and reduced incidence of autoimmune hepatitis. The main metabolic disorder contributing to liver failure was Wolcott Rallison syndrome (a syndrome commonly seen in the Arab world and seen in children of consanguineous marriage). The presenting features and biochemical tests alluded to different aetiologies and can help target investigations. The Mortality rate was high in our group, we feel this can be secondary to the different aetiology spectrum in our group in addition to lack of availability of liver transplantation in the UAE, and the need for children with ALF to travel for transplantation.

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Nutritional care for infants with biliary atresia after Kasai hepatoportoenterostomy: regular or aggressive?

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Objectives and Study: Infants with biliary atresia (BA) frequently have an impaired nutritional status at the moment of Kasai hepatoportoenterostomy (KPE). Impaired nutritional status and growth may exert negative effects on short- and long-term outcomes. To obtain more epidemiological and mechanistic insights and to identify areas for improvement in care, we analysed in detail the perioperative nutritional status and growth of infants with BA undergoing KPE in our tertiary referral centre.

Methods: We retrospectively included all infants in the Netherlands with BA undergoing KPE between 1/2015 and 4/2017. Anthropometric measurements, nutritional status and clinical data at admission until eight weeks post-surgery were extracted from patient records. Nutritional assessment included calorie and protein intake, type of nutrition formula and nature of nutritional care: regular [breast and/or bottle feeding] versus aggressive [(partly) nasogastric drip or parenteral feeding]. To compare the feeding intake over the study period and between patients, we defined feeding intake to be adequate when it reached both 117 kcal/kg/day and 2.7 g protein/kg/day, irrespective of the route of administration.

Results: We included 30 infants (8M/22F), with a mean age at KPE of 61 days. At the moment of admission for KPE, the mean z-scores for mid upper arm circumference (MUAC) and weight were below zero (MUAC: p< 0.001, 95%CI -2.01; -1.43 and weight: p=0.003, 95%CI -1.11; -0.26 resp.). Only at four weeks post-surgery, the mean MUAC and weight z-scores reached the z-scores measured preoperatively. Continuously, up to eight weeks after admission, z-scores for MUAC were lower than for weight (ρ<0.05). Z-scores for weight correlated poorly with those of MUAC (rho value at admission and at eight weeks, 0.51 and 0.21 resp.). Fifty percent, 77%, 80% and 62% of infants met adequate feeding intake at admission, one, four and eight weeks, respectively. At admission, all infants received breast milk or standard infant formula. At eight weeks post-surgery, all infants were fed with specialized formula with 49% medium chain triglycerides except for one exclusively breastfed infant. At one week post-surgery, 34% of infants received regular and 66% aggressive nutritional care, corresponding with 43% and 84% of them reaching the predefined adequate feeding intake (p=0.06).
Conclusions: Infants with BA are frequently malnourished at the moment of KPE. Our data strongly indicate that MUAC reflects the state of (mal)nutrition more accurately than body weight, possibly due to organomegaly and/or ascites affecting the latter. A major fraction of these infants, in particular those on regular, non-assisted nutritional care, do not obtain adequate nutritional intake in the early postoperative phase. Aggressive postoperative nutritional care seems warranted to reach adequate nutritional intake in infants with biliary atresia.


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Liver function abnormalities in paediatric emergency department; etiologies, recovery time of liver function and length of stay in hospital

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Objectives and Study: Liver function test abnormality is frequently noted in children especially in emergency departments. There is limited data about the symptoms on admission, etiology recovery time of abnormal liver function and length of stay (LOS) in hospital.

Method: Children with elevated transaminases, who were followed in our observation unit of paediatric emergency department between January 2016 and January 2017, were included. The elevated AST and ALT were defined as values above of 60 IU/L and 45 IU/L respectively. The clinical data was retrospectively collected from electronic medical records.

Results: 89 children included in the study. The median age was 36 months (IQR: 8-97 months). This group comprised of 39 (43.8%) females and 50 (56.2%) males. On admission, the most common complaints were vomiting (34.8%), fever (30.3%) and abdominal pain (28.1%). The most common causes of the elevated transaminases were non-specific hepatitis in 24 (26.9%), gastrointestinal tract infections in 12 (13.5%), drug-induced liver injury in 9 (10.1%), upper respiratory tract infection (URTI) in 9 (10.1%). The other underlying causes were metabolic disease in 7 (7.9%), Epstein-Barr-Virus infection in 6 (6.7%), and lower respiratory tract infection in 6 (6.7%), heart failure in 3 (3.4%), Hepatitis A infection in 3 (3.4%) and other etiologies in 10 (11.2%) cases. The recovery time of the abnormal liver function was 4.5 days (IQR: 2.0-13.7). Hospitalisation time of patients was 3.6±9.2 days. There was no significant difference in recovery time of elevated transaminases between idiopathic cases and the others (p=0.277), but LOS in hospital was shorter in idiopathic cases when compared with the others (p=0.021). Also the patients with URTI had shorter LOS in hospital when compared with the other reasons (p=0.017) and recovery time was not significantly different from other etiologies (p=0.826).

Conclusion: Recovery time information of abnormal liver function in some disease subgroups may help the physician to perform better clinical consultation for patients and their parents.
Diverse mutations and different clinical outcomes in children with progressive intrahepatic cholestasis

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Objectives and Study: Progressive Familial Intrahepatic Cholestasis (PFIC) defines several rare disorders of hepatocanalicular transport. Most common presentation is neonatal cholestasis with pruritus in the absence of elevated GGT in subtypes I and II, but type III. Recently further subtypes are described based on genetic and clinical studies. In this study we aimed to analyse the impact of different genetic mutations on clinical outcome in classical PFIC diseases.

Method: Chart analysis of 15 children with genetically confirmed PFIC disease followed at a single tertiary centre between 2006 and 2017, was carried out. Children with a clinical diagnosis of PFIC, but absent genetic analysis were excluded from the study. Data including age, symptoms, laboratory results including histopathological findings, CHILD Pugh and PELD scores at presentation and clinical follow-up were retrospectively reviewed together with the results of PFIC gene analysis.

Results: Mean age at presentation of 15 children (7 girls 46%) was 2.9 months (range 1.5- 6 months). Most common complaints at presentation were jaundice (n=14, 93%) and pruritus (n=7, 50%). Two children (13%) had previous history of intracranial bleeding at the time of diagnosis. Subtypes of PFIC were as follows: 1 PFIC type I (6.6%), 10 PFIC type II (66.6%), and 4 PFIC type III (26.6%). Seven patients needed surgery: Five (4 PFIC II, 1 PFIC III) underwent partial internal biliary diversion (33.3%), three (2 PFIC II, 1 PFIC III) had liver transplant (LTx) (20%). Only one child with biliary diversion underwent LTx.

Molecular genetic analysis showed either homozygous mutations or compound heterozygosity, associated with polymorphisms in any PFIC gene. PFIC type I patient had homozygous mutation of ATP8B1 and drug-induced polymorphism at the ABCB11 gene, and displayed mild to moderate liver disease. In 8 children (60%) out of 10 with PFIC type II, homozygous mutation in ABCB11 gene was found. One child with PFIC type II had compound heterozygous mutation and the last one had ABCB11 and ABCB11 polymorphism. In 3 children with homozygous mutations with ABCB11 mutation, polymorphisms of ABCB11 and ABCB4 were determined. These 3 children had more severe disease compared to the children, who did not have polymorphisms in the ABCB11 and ABCB4 genes. One of these 3 children died (PELD 36, CHILD C) awaiting LTx due to chronic liver disease complications, the other had severe metabolic bone disease with fractures and pruritus and underwent living-related LTx (PELD 6, CHILD A) at two years of age. The third child, awaiting LTx (PELD score 16, CHILD B) had intracranial bleeding at presentation. She has severe neurological and ophthalmological complications due to vitamin A and E deficiencies despite appropriate prophylaxis. The PFIC II patient with biliary diversion and subsequent LTx has polymorphisms in ABCB4 and ABCB11 genes. Among PFIC type III patients, 2 children had homozygous ABCB4 mutations, 2 had compound heterozygous mutations. In this group there was one child who underwent LTx and one with biliary diversion.

Conclusion: Our PFIC cohort show a wide range of genetic diversity. Presence of of ABCB11 and ABCB4 polymorphisms with or without homozygous mutations in ABCB11 gene may predict a worse outcome compared to the rest of the children.

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Objectives and Study: Vascular disorders of the liver might be caused by congenital anomalies, coagulopathies and by chronic liver disease (CLD). They are associated with severe complications. Children with prehepatic portal vein obstruction are recommended MesoRex bypass (MRB) for prophylaxis of variceal bleeding and other complications. Partial splenic embolization is an adjunctive treatment option in portal hypertension with hypersplenism. Transjugular intrahepatic portosystemic shunt (TIPS) may be a treatment option in children with gastrointestinal haemorrhage and ascites unresponsive to other treatment. Closure of congenital portosystemic shunts (CPSS) should be considered early to prevent development of hepatopulmonary syndrome, pulmonary hypertension and chronic hyperammonemia. Vascular complications after liver transplantation (LT), especially in small children, may require interventions. To improve our evaluation, management and follow up of this patient group; a multidisciplinary team was set up at our tertiary center for pediatric hepatology. The aim of this study was to evaluate the results of first two years with this team.

Method: The team consists of paediatric hepatologists, paediatric coagulation specialist, interventional radiologist, paediatric radiologist, paediatric hepatology nurse and patient coordinator. The team collaborates with a paediatric abdominal-and transplant surgeon, with expertise in the MRB, at another center. Charts of all patients evaluated by the team January 2015-November 2017 were reviewed. In case of intervention platelet count, ammonium level and spleen size, before and after the procedure, were recorded.

Results: 28 patients (10 girls, 18 boys), median age 8.9 yrs. (23 days-17.4 years) were evaluated. Diagnoses were CPSS (8 patients), chronic prehepatic portal vein thrombosis/obliteration (8), CLD (6), vascular complication post liver transplantation (5), Budd Chiari (1). 15 patients underwent vascular interventions, see table below. One patient had a TIPS followed by partial spleen embolization (included in two groups). The results of the procedures on mean platelet count, ammonium level and spleen size are included in the table. Increase in mean platelet count, reduction in mean ammonium level and decrease in mean spleen size were seen to various extent in the MRB-, splenic embolization- and TIPS-groups. Plug occlusion of CPSS resulted in lower ammonium levels. Statistics not calculated due to limited number of patients. The patients who developed MRB stenosis and TIPS occlusion could be successfully treated with stent placement and TIPS revision, respectively.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of patients</th>
<th>Age (mean)</th>
<th>Before procedure (mean)</th>
<th>After procedure (mean)</th>
<th>Complications (number of patients)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Platelet count x10(9)/L</td>
<td>Ammonium mikromol/L</td>
<td>Spleen size cm</td>
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<td>Meso-Rex bypass</td>
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<td>No shunt flow</td>
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<td>1) Stenosis</td>
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<td>Stent occlusion</td>
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<td>CPSS closure</td>
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</table>

[Table: Results of the procedures]

**Conclusion:** A multidisciplinary team for vascular liver disease can be an efficient way to structure the evaluation and treatment of patients with hepatic vascular disorders and optimize care and outcome.

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HEPATOLOGY - General Hepatology

H-P-018

Risk factors and outcome of variceal haemorrhage following Kasai portoenterostomy in children with biliary atresia - experience from a single tertiary center

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Objectives and Study: Variceal haemorrhage (VH) is a potentially fatal complication in children with biliary atresia (BA) and portal hypertension (PH), and medical and endoscopic management can be challenging during the acute stage. Endoscopic treatment and liver transplantation have improved overall outcome in BA patients who have developed VH, however primary endoscopic surveillance and prophylactic therapy for the prevention of VH remain controversial. The aim of this study is to evaluate the risk factors associated with VH in BA, and the long-term outcome following the first episode of VH at a single tertiary paediatric centre.

Method: Retrospective review of medical records was performed of all patients diagnosed with BA from 1987-2016. Cases of VH were confirmed on endoscopic assessment in patients who presented with upper gastrointestinal bleeding. Treatment of VH was based on standardised department protocol consisting of octreotide, proton pump inhibitor, sucralfate, and acute and secondary prophylactic endoscopic therapy. Surgical history, ultrasonographic data and laboratory parameters, including haematologic and biochemical markers in the preceding 3 months before the first VH and at most recent follow-up were analysed.

Results: Total of 76 patients were diagnosed with BA with median follow-up duration of 7 years (range: 0.5 - 30). Four patients were excluded from analysis (2 lost to follow-up, 2 did not undergo Kasai surgery). Majority of patients were of Chinese ethnicity (66%) and 47% were male. Median age at Kasai portoenterostomy (KP) was 54 days (range: 29-119) and jaundice clearance rate at 6 months was 57%. PH developed in 74% of our study cohort. VH occurred in 16 patients of whom 12 had one episode and 4 had recurrent bleeds. Median age at first onset of VH was 5.5 years (range: 0.3 - 19). Patients who developed VH were more likely to have established cirrhosis at the time of KP compared to those with no VH (50% vs 5.1%, p=0.001), but no difference was observed in proportion of patients who had KP after 60 days of life (47% vs 38%, p=0.526), jaundice clearance at 6 months (43% vs 62%, p=0.199) or history of cholangitis (63% vs 69%, p=0.620) between the 2 groups. Variables that were significantly associated with the onset of first VH were platelet count< 100x10⁹/L (OR 31.3; 95CI: 0.5-21.2, p=0.012), aspartate transaminase (AST)>100U/L (OR 24.3; 95CI: 1.7-344.5, p=0.018), and ultrasonographic findings of increasing spleen size >2cm per year (OR 5.3; 95CI: 1.3-22.5, p=0.023), ascites (OR 4.7; 95CI: 1.3-16.6, p=0.018) and varices (OR 4.1; 95CI: 1.2-14.4, p=0.028). Serum albumin, bilirubin and haemoglobin levels were not found to be predictive of VH. Median overall survival (OS) following the first VH was 7.5 years (range: 0.2-25). A trend towards poorer long-term OS was observed in patients with VH who remained non-transplanted compared to patients without VH, although statistical significance was not attained.
[Survival analysis of BA patients stratified according to development of VH and transplant status.]

**Conclusion:** BA patients with the risk factors of platelet count $<100 \times 10^9$/L, AST$>100$U/L, and ultrasonographic evidence of rapidly increasing spleen size (>2cm/year), ascites and/or varices are at significantly higher risk of VH; primary prophylactic endoscopic therapy may benefit this subgroup of patients in preventing the onset of VH.

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Neonatal autoimmune hepatitis. A series of four case reports

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Objective: To describe the clinical presentation and evolution of 4 patients with autoimmune hepatitis with neonatal debut.

Methods: A case series of 4 patients with neonatal autoimmune hepatitis, attended at Instituto Nacional de Pediatria, Mexico, between january 2016 and december 2017.

Results:

Case 1: A 4-month-old female, was admitted with history of jaundice since 5th day of life. On admission, she had jaundice and hepatosplenomegaly. Laboratory test showed elevated liver function tests, hypoalbuminemia and elevated serum IgG and blood cell counts were normal (Table 1). Viral panel was positive CMV IgG. Auto antibodies ANA and antiLKM1 were positive. Liver ultrasound showed no focal lesions and no gall stone or biliary dilatation. Biopsies showed giant cell hepatitis with lymphocytic infiltrate and fibrosis. Azathioprine and prednisone were started with good clinical outcome at 3 months of follow up.

Case 2: A 2-month-old male, was seen at INP because of jaundice since birth. Physical examination revealed jaundice and hepatosplenomegaly. Laboratory investigations showed elevated liver function tests, elevated serum IgG and blood cell counts were normal (Table 1). Viral panel was negative. Autoimmune panel revealed that ANA and ASMA were negative, whereas antiLKM1 was high. Liver ultrasonography was normal. Histologic findings with interface hepatitis. Azathioprine and prednisone were initiated with good clinical outcome at 1st month of initiated treatment.

Case 3: A 2-month-old male, presented with diarrhea, dehydration, hypoglycemia and upper respiratory tract infection, without jaundice since 20th day of life. On examination, he had respiratory distress and hepatomegaly. Laboratory tests showed normal blood cell counts, elevated liver function tests, hypoalbuminemia, prolonged hemostatic screening tests and elevated serum IgG (Table 1). ASMA and ANA were negative. AntiLKM1 was positive. Liver ultrasound was normal. Histologic findings with extensive hepatocellular necrosis, pericellular fibrosis and lymphocytic infiltrate. Prednisone and azathioprine were initiated with favorable clinical outcome at 2 months of treatment.

Case 4: A 1-month-old male, was admitted to our institution because of hematemesis and melena. On admission, he had hepatosplenomegaly. Laboratory tests showed normal blood cell counts, elevated liver function tests, hypoalbuminemia and elevated serum IgG (Table 1). Liver ultrasound was normal. Upper endoscopy without esophageal varices. Viral panel was negative. Ig G was 960 mg/dl. ASMA and ANA were negative and antiLKM1 was high. Histologic findings showed periportal lymphocytic infiltrate, extending into the liver parenchyma, without portal fibrosis. Prednisone and azathioprine were started with a good clinical outcome at 1st month of treatment.
**Variable** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4**  
--- | --- | --- | --- | ---  
Clinical presentation | Cholestatic syndrome | Cholestatic syndrome | Acute liver failure | Upper gastrointestinal bleeding  
TB/DB (mg/dl) | 7.5/4.3 | 9.2/5.6 | 1.86/0.97 | 0.54/0.09  
ALT (UI/l) | 113 | 222 | 159 | 178  
Prothrombin activity (%) | 87 | 101 | Unable to clott | 127  
Albumin (g/dl) | 3.2 | 4 | 2.8 | 2.8  
Total Ig G (mg/dl) | 1450 | 381 | 867 | 960  
AntiLKM1 | Positive (24.79) | Positive (44) | Positive (33.84) | Positive (33,47)  
ASMA | Negative | Negative | Negative | Negative  
Histologic findings | Giant cell hepatitis with fibrosis and lymphocyte infiltration. | Interface hepatitis with lymphocyte infiltration. | Extensive hepatocellular necrosis, pericellular fibrosis and lymphocytic infiltrate | Periportal lymphocytic infiltrate, extending into the liver parenchyma, without portal fibrosis  

**TABLE1. Symptoms, laboratory test histologic find**

**Conclusions:** To our knowledge, hepatitis autoimmune has not been reported previously in the neonatal period. The diagnosis of autoimmune hepatitis is established with clinical symptoms, laboratory tests and histologic findings. The treatment should be established as soon as possible, avoiding progression and complications. All cases had clinical manifestations during their first month of life, antiLKM1 antibodies positive, IgG elevation and favorable response to immunosuppressive treatment.

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Acute colangitis in patients with biliary atresia after Kasai surgery - case study of 30 years (partial results)

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Objectives and Study: Biliary atresia (BA) can lead to early hepatic cirrhosis and need for liver transplantation. The initial treatment is Kasai’s surgery, which in the postoperative period may have complications, such as cholangitis. The goal of this study is to investigate the frequency of cholangitis episodes after Kasai, to relate bile flow restoration with the occurrence of cholangitis, to evaluate gamaglutamyltransferase (GGT) and alkaline phosphatase (ALP) in the diagnosis of cholangitis and to identify initial symptoms.

Method: A retrospective and cross-sectional study was performed by analyzing the medical records of patients submitted to Kasai between 1985 and 2015. Patients were classified into two groups in relation to biliary flow restoration: I - absence or little restoration of biliary flow (no decrease in bilirubin level direct after surgery or fall below 50%); II - average or good bile flow restoration (drop greater than or equal to 50% of the level of direct bilirubin after surgery). The diagnosis of cholangitis was based on clinical, laboratory and / or liver biopsy abnormalities.

Results: Thirty-six patients was enrolled, the average age at the time of Kasai was 86.25 days, with predominance in girls (25/36). Twenty one patients had cholangitis, 13 of these had recurrent episodes, total of 48 episodes of cholangitis. In relation to bile flow restoration: 21 patients who presented cholangitis, 11 had average or good restoration of biliary flow and 10 patients did not. Of the 13 patients who did not have cholangitis, 4 had good bile flow restoration and 9 absence or little restoration of biliary flow, without statistically significant difference (p= 0.21 - $\chi^2$ test). 26 patients had their first episode of cholangitis in the first year after surgery. Levels of GGT ranged from a median of 335 to 447 and alkaline and ALP ranged from a median of 552 to 676. This last one was not statistically significant. 40/48 episodes of cholangitis presented fever, 34/48 jaundice, 22/48 hepatomegaly, 19/48 choluria, 16/48 acholic / hypocholic stools, and 16/48 presented splenomegaly.

Conclusion: The frequency of cholangitis after Kasai’s surgery was high (60%), most of them in the first year after surgery. There was no positive relation between the occurrence of cholangitis and restoration of the bile flow, during the episodes there was a significant increase of the GGT and fever and jaundice were the most prevalent signs of cholangitis.

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**Objectives and Study:** Giant cell hepatitis with autoimmune haemolytic anemia is a very rare disease with poor prognosis, characterized by early onset, severe clinical manifestations, including immune hemolytic anemia and hepatitis with cholestasis, probable autoimmune etiology. It is described in the age group of infants, manifesting with hemolytic anemia, positive direct coombs and hepatocytic lesion with giant-cell transformation. Therapy is with immunosuppressive drugs and, in some cases, liver transplantation. It is more serious and rarer than autoimmune hepatitis type 1 or 2. The goal of this report is alerting for the diagnosis of this disease and some different characteristics of the literature.

**Method:** Description of the case experienced by the authors.

**Results:** A 3 year-old boy sought emergency due to cough and coryza for 15 days, using acebrofilina and ibuprofen, and, for 4 days jaundice, myalgia and vomiting. Previous history of myelitis and immune thrombocytopenic purpura (resolved) and prior elevation of aminotransferases, in declining, without jaundice. Blood count (Hb 9.2g / dL), alanine aminotransferase (ALT) = 1038U/L, aspartate aminotransferase (AST) = 806U/L, alkaline phosphatase (ALP) = 378U / L, gammaglutamyltransferase = 90U / L, total bilirubin = 8.68mg / dL, bilirubin indirect = 4,1mg/dL, normal coagulation, reticulocytes = 2%, negative serologies for hepatitis A, B, C, mononucleosis, cytomegalovirus, toxoplasmosis; Non-reactive FAN; negative autoantibodies; gamma globulin of 0.86g/dL, normal serum complement (C3: 1.74mg / dL and C4: 0.23); normal alpha1 antitrypsin, alphafetoprotein, ceruloplasmin and immunoglobulin dosage; abdominal ultrasonography: mild splenomegaly. Laboratory evaluation revealed marked anemia (hemoglobin fell in 24h for 2,1g/dL) with positive direct coombs, hemodynamic and respiratory instability, worsening of hepatitis, with a marked increase in indirect bilirubin (BI = 21.83mg/dL / BT = 26.2mg/dL), RNI enlargement (1.81) and reticulocytosis. Suspecting giant-cell hepatitis with autoimmune hemolytic anemia, he underwent methylprednisolone pulse therapy, but he died in 72h. Hepatic biopsy revealed gigantocellular transformation of hepatocytes.

**Conclusion:** It is possible for this disease to appear in children over two years old; Hepatitis may precede haemolytic anaemia;
It is a serious disease requiring rapid diagnosis, immunosuppressive treatment and, in some cases, intensive therapy.

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Objectives and Study: Biliary atresia (BA), an inflammatory obliterative cholangiopathy of unknown etiology, is the principal indication for paediatric liver transplantation. Several studies showed that about 10% of patients surviving with native liver has no clinical and biochemical evidence of chronic liver disease (CLD) after 5 or more years from Kasai portoenterostomy (KP), but most of the patients have fibrosis at biopsy. Scant information about magnetic resonance cholangiography (MRC) findings in these patients is available. The aim of our study was to evaluate MRC aspects in children with BA surviving with their native liver and with normal bilirubin values 5 years after KP.

Method: We retrospectively evaluated all patients with BA referred to our Pediatric Liver Unit between 1983 and 2016. Inclusion criteria were: BA diagnosis confirmed by intraoperative cholangiography, survival with native liver and normal bilirubin values 5 years after KP; MRC performed in the last three years of follow-up. Clinical and laboratory data of the patients were collected. Radiographic signs of liver and biliary disease were evaluated on ultrasound and MRC.

Results: 112 patients with BA were observed: 68 patients underwent liver transplantation and 44 (39.3%) survived with native liver. Among the latter patients, 25 (14 males) fulfilled the inclusion criteria. Median duration of observation was 11.5 years (range 6-27). At the last follow up, median patients age was 11.75 (range 5.7-27.1) years and only 6 (24%) showed clinical and laboratory signs of portal hypertension and hypersplenism. Only 2 (8%) showed variceal bleeding. During the entire follow-up, 19 (76%) of 25 patients did not experience any episode of cholangitis. All the enrolled patients underwent abdominal ultrasound in the last year: signs of liver cirrhosis were recorded in 12 (48%) cases, fibrosis in 17 (68%). MRC showed: hepatomegaly in 17 (68%) cases, inhomogeneous liver structure in 24 (96%). 14 (56%) patients had signs of liver cirrhosis, 15 (60%) fibrosis, 10 (40%) rosary appearance of biliary tract. All patients exhibited irregular caliber of intrahepatic bile ducts. Statistical analysis of cholangiographic findings highlighted no correlation between hypersplenism and biliary tract with a rosary appearance.

Conclusion: One half of patients with BA surviving with native liver and with normal bilirubin values 5 years after KP present signs of cirrhosis at MRC. Further studies are needed to define the meaning of these results and their impact on the long term outcome of survivors with native liver.

References:

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Hepatic disease in cystic fibrosis. A look at liver histology in liver transplanted patients

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Introduction: The hepatic complication in Cystic Fibrosis (HCCF) causes important morbidity and mortality. Hepatic transplantation arise as a therapeutic alternative. Liver transplantation histological pattern has not been described.

Objective: Describe the hepatic histology of patients transplanted with Cystic Fibrosis (CF).

Methods and material: A retrospective, descriptive, observational study. In a transplant list of a multicenter of 1253 pediatric liver patients transplanted from 1996 to 2016. We transplanted 10 patients with CF (0.7%) the median age for the transplant was 12 years. Nine livers explanted were studied. After weighing and recording the appearance of the external surface besides measuring the liver, at least four different sections of the hepatic portal were taken. Three different sections of the right and left lobes were sent to pathology unit, as well as caudate quadrate and gallbladder. Clinical, imaging and hepatic pathology characteristics were analyzed.

Results: Three patients presented ALT in the normal range, 6 had hypertransaminemia (mean: 199.2 IU). Five patients were hypoalbuminemic. All of them presented severe splenomegaly and thrombocytopenia (mean: 75877 (uL). All patients had portal hypertension and 7 had esophageal varices, but none had variceal bleeding. All liver ultrasound showed heterogeneous echogenicity. Explant liver of all patients did not show patterns of complete cirrhotic-type regenerative nodules but we found mild to moderate septal fibrosis (F2-F3) alongside with areas of incomplete septal cirrhosis. We saw vascular changes like obliterative venopathy, portal vein, shunt vessels associated with dense portal fibrosis and lack of portal tract inflammation. In liver parenchyma of livers explanted we found areas of Nodular Regenerative Hyperplasia (NRH) close to megasinusoides. Another finding was few isolated arteries unaccompanied by a portal vein or a bile duct. Some large hepatic veins had segmental sclerotic changes. At follow-up, 2 post transplanted patients died 1.8 years and 12 years after liver transplant.

Conclusion: The liver explants showed macronodules associated with severe fibrosis and different types of vascular lesions mainly, obliterative venopathy portal and vein shunt vessels. This finding could be the most important cause of portal hypertension. We propose that cause of portal hypertension in CF be considered a vascular disease rather than a biliary cirrhosis.

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Kidneys malformations in Alagille syndrome patients

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Objectives and Study: Kidneys malformations in Alagille syndrome patients are characterized by variability of congenital and acquired anomalies. The ultrasound changes frequency varies widely as well and, according to most authors, these changes are not a mandatory criteria for diagnosis. We hypothesized, that the renal anomalies occurs in the majority of patients with Alagille syndrome and could be one of the main criteria of the disease along with cholestasis syndrome, skeletal anomalies, heart malformations and ophthalmologic findings. The aim of this study was to define frequency and spectrum of renal echographic changes in Alagille syndrome children.

Patients/Methods: Fifty infants with Alagille syndrome were under observation during the first year of life in National Medical Research Center for Obstetrics, Gynecology and Perinatology, Russian Ministry of Health, Pediatric Outpatient Department. Echographic examination of the kidneys was carried out by convex ultrasound transducer with a frequency of 3.5-5.0 MHz and an additional linear transducer with a frequency of 10-14 MHz using Echographe G.E Voluson E8 Expert and Toshiba Apio XG each 1-2 months.

Results: 87% patients had small up to 1.5-3 mm cysts in renal pyramids and renal cortex; 70% had increased echogenicity of renal cortex; 64% had disordered corticomedullary differentiation in renal parenchima, particular reduced number of renal lobes and pyramids to 4 or fewer on cut surface. 12% pts had renal hypoplasia. Doppler data showed increased resistive index >0.8 of renal arteries branches in 20-38% children. The frequency of the main ultrasound signs depended on the patient´s age: first signs were identified at 1 month, and their occurrence increased to 3 months with the maximum severity at 1 year of life.

Conclusion: In our study about 90% of children with Alagille syndrome had some echographic signs of renal parenchyma injury. This fact makes kidneys anomalies one of the main criteria for the Alagille syndrome.
Evaluation of King’s variceal prediction score as a marker of portal hypertension in children with Chronic liver diseases

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Objectives and Study: Variceal bleeding is one of the chronic liver disease complications in children which can be life threatening. There is limited useful tool to selection the children with chronic liver disease for clinically significant varices who will benefit from upper endoscopy.

Method: This study include all Patients of either sex, aged less than 18 years old with diagnosis of chronic liver disease (CLD) independently of etiology. All cases underwent esophagogastroduodenoscopy (EGD) for evaluation of esophageal varice presented in Pediatric Gastroenterology (GI) ward in Nemazee-Hospital a referral center in south of Iran affiliated to Shiraz University of Medical Science. Patient demographies, etiology and complications of liver disease with clinical, biochemical and radiological data were collected. Kings variceal prediction score index and other prediction indices were calculated.

Results: Data on 104 patient were collected; 17.3% had Wilson disease and 16% had biliary atresia. Twenty seven (26%) children present with gastrointestinal bleeding and overall 62 (59.6%) had clinically significant (grade II- III) varices. Kings variceal prediction score (K-VaPS), Clinical prediction rule (CPR), Varices prediction rules (VPR), platelet count/spleen diameter ratio and platelet count/equivalent adult spleen diameter ratio had at optimal cut-off sensitivity and specificity of 51.61% and 69.05%, 43.55% and 73.81%, 51.61% and 73.81%, 53.33% and 71.43%, 51.61% and 69.05% respectively. Clinical prediction rules (CPR) had a favourable AUROC of 0.699 (0.59-0.80) compared to Kings variceal prediction score 0.646 (0.53-0.75). Kings variceal prediction score cut-off of 45.8 yielded a sensitivity and specificity of 51.61% and 69.05% and a positive and negative predictive value of 71.1% and 49.15% respectively.

Conclusion: King variceal prediction score is an appropriate substitute for endoscopy and can be useful tool in the screening of clinically significant varices in the children with chronic liver disease who will benefit from a surveillance endoscopy.

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Gallbladder polyps: Rare lesions in pediatric population

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Objectives: Gallbladder polyps (GPs) are elevations of the gallbladder wall that project into the lumen. Most GPs are benign. It is clinically significant that the possibility of developing cancer is increased when the lesion is more than 1 cm in diameter and when it has an adenomatous structure. Most of the patients have no clinical sign. They are usually detected on abdominal ultrasonography (USG) incidentally. In contrast to adults, polypoid lesions of the gallbladder in children have been reported rarely. We described 15 children with gallbladder polyps, who were followed in one center during the last 5 years.

Materials and methods: We evaluated the patients with GPs between October 2012 and October 2017, retrospectively. There were 15 patients in our unit who were diagnosed with GPs via ultrasonography. Demographic findings, liver function tests, alpha fetoprotein (AFP) levels, lipid panels, number and diameter of the polyps were evaluated.

Results: The mean age was 13.7±4.1 years (range; 1.6-17.7 years), 12 patients (80%) were female. The mean body mass index of the patients was 21.2±5.1 kg/m2 and there were three patients who were overweight. The most common presenting symptom in order to apply abdominal USG, was abdominal pain in 11 (73%) patients. None of the patients had any co-morbid disease and positive family history. Follow-up duration was 11.2 ± 1.4 months (range; 3-26 months). The mean diameter of the polyps was 4 mm (range; 2-9 mm) as measured by the first ultrasonography. Four patients had more than one polyp, while the remainders had one, each (Figure). The laboratory tests were all normal, including complete blood count, liver function tests, alpha fetoprotein and lipid profile. There was no significant change in size of polyps between the first and last USG. One of the patients who had 5 GPs, (biggest one was 9 mm) underwent a cholecystectomy. The histopathological study showed hamartomatous polyps. Other patients continue to be followed without any problems.

Conclusion: Polypoid lesions of the gallbladder mucosa have been described in adults mostly. These lesions have been reported rarely in children. Because USG is the preferred initial imaging modality of the patients with abdominal pain, more GPs are being identified in childhood period. It is postulated that the risky conditions for developing GPs in children are Peutz-Jeghers syndrome, leucodystrophy and pancreaticobiliary malunion. However, there were not any of them in our patients. The main risk factors for malignant transformation include; size (>10 mm) and number (single or sessile) and also, they are associated with wall thickening, gallstone formation, adenomatous features, rapid growth and old age (>52) in adults; but there are no certain clues in children. Asymptomatic cases should be maintained under ultrasound surveillance.
[Ultrasonographic view of a 4 mm polyp at the gallbladder corpus.]

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Objectives and Study: Crigler-Najjar (CN) is a monogenetic defect of bilirubin conjugation due to the absence of bilirubin UDP-glucuronosyltransferase (UGT), and without appropriate therapy can lead to irreversible bilirubin-induced brain injury (kernicterus) at any age. Although phototherapy (PT) reduces bilirubin and the risk for kernicterus, most patients eventually require liver transplant for definitive treatment. Gene replacement therapy for the missing UGT enzyme may offer an alternative treatment for CN patients. We initiated a longitudinal prospective study (LUSTRO) to profile the baseline clinical characteristics of CN subjects who have bi-allelic mutations of UGT1A1, aged ≥1 year of age, requiring ≥6 hours daily PT. Patients in LUSTRO are intended to roll over to a Phase 1/2 intervention study (VALENS) with AT342, an investigational AAV8 gene therapy product containing the UGT1A1 gene.

Method: Individuals eligible for LUSTRO will be followed for up to two years. Those who received or planned to receive partial liver, whole liver, or hepatocyte transplant are excluded. All study subjects used a custom high-power blue LED PT system designed to provide maximum and uniform lighting. Daily illumination time in hours was collected by subject diary reports after baseline irradiance measures and patient distance from their PT system was collected. Bilirubin levels were assessed by weekly blood draws for 12 weeks followed by bi-monthly assessments for the duration of the study. At Week 6, subjects underwent intensive sampling over 24-hours for a bilirubin area under the curve (AUC) value.

Results: As of October 2017, three CN subjects (Table 1) have been followed in the United States for 26, 26, and 18 weeks. Two males (ages 11 and 12 years) are homozygous for UGT1A1 c.222C>A, which introduces a premature stop codon in UGT. One female, age 16 years, has a short duplication that results in a frameshift after Arg209 and premature stop codon at amino acid position 259. Subjects used their PT systems for a daily average of 10.7, 9.4, and 10.8 hours and had markedly elevated average bilirubin levels of 195, 251, and 284 µmol/L, respectively, with high intra-subject variability. The highest bilirubin during the study period was 340 µmol/L (Patient 3). No subject required plasmapheresis or exchange transfusion.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Yrs), Gender M/F</th>
<th>UGTA1A1 Mutations</th>
<th>Observation interval (Weeks)</th>
<th>Phototherapy daily average (hrs)[range]</th>
<th>Total Bilirubin average(µmol/L) [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11, M</td>
<td>c.222C&gt;A;p.Tyr74*</td>
<td>26</td>
<td>10.73[8-13]</td>
<td>195 [148-253]</td>
</tr>
</tbody>
</table>

Conclusion: Despite aggressive management with daily PT, the three participants enrolled in LUSTRO had variable yet consistently high unconjugated serum bilirubin levels that reached potentially neurotoxic range (e.g. up to 340 µmol/L). Such patients are candidates for gene replacement therapy with AT342, an investigational AAV8-delivered gene transfer therapy intended for
CN subjects aged ≥1 year. VALENS is a randomized, open-label, ascending-dose, delayed treatment concurrent control study to evaluate the safety and efficacy of AT342 in patients with CN.

**Disclosure of interest:** Prof Anil Dhawan - on the Advisory board Suyash Prasad, Dexter Kennedy, Mo Nourselai are employees of Audentes Therapeutics Inc.

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**Objectives and Study:** Wilson's disease (WD) is an autosomal recessive inherited disorder of copper excretion, caused by mutations of the ATP7B gene. All WD patients need life-long treatment. The currently available drugs are D-Penicillamine, Trientine and Zinc. It is already known that zinc therapy may be responsible for increased levels of serum amylase and lipase. On the other hand, episodes of overt pancreatitis are not reported during this treatment. Therefore currently zinc is not considered cause of pancreatic damage. Aim of our study was to evaluate the relationship between zinc therapy and serum levels of pancreatic enzymes and to investigate exocrine and endocrine pancreatic function in WD patients on long-term zinc salts therapy.

**Method:** Inclusion criteria were: established diagnosis of WD, available pancreatic data, exclusive zinc therapy and at least three years of follow-up. We retrospectively evaluated the pancreatic enzymes in WD patients before and during treatment and at the end of follow up. As for exocrine function, steatocrit and fecal elastase1 were tested; endocrine function was evaluated by glycemia, insulinemia, Homa-ir and glycated hemoglobin (Hb1Ac) at the end of follow-up. We also considered the occurrence of pancreatitis and relationship between pancreatic enzymes levels and urinary zinc levels. Statistical analysis was performed using the SPSS software for Mac.

**Results:** We evaluated 53 WD patients and 42 patients (23 M; median age: 21.9 ± 8 years, median follow-up duration: 17.2 ± 12.4 years) were enrolled according to inclusion criteria. On the basis of amylase, p-amylase and lipase serum levels at the end of follow-up, two following groups were identified: 17 patients (40.5%) with hyperamylasemia and/or hyperlipasemia (HA/HL group) and 25 patients with normal enzymes (n-HA/n-HL group). No significant difference was documented between the two groups for age at diagnosis, duration of follow-up, liver enzymes levels during and at the end of follow-up. A positive correlation was demonstrated between pancreatic enzymes and urinary zinc levels. As for exocrine function, 3 patients (7.1%) showed low fecal elastase1 values compatible with a mild pancreatic insufficiency and the HA/HL group showed lower elastase mean values than the nHA/n-HL group (p= 0.02). Four patients (9.5%) showed abnormal levels of steatocrit, but no significant difference between the two groups was found. Hb1Ac, insulinemia and Homa-ir values were not significantly different in the 2 groups. All patients had normal fasting glycemia values but a significant difference between the two groups was observed (p=0.03). A single patient experienced two episodes of acute pancreatitis in the absence of the common causes of pancreatitis other than zinc therapy.

**Conclusion:** Although an overt pancreatic damage is rarely present in WD patients on long-time zinc therapy, a careful evaluation of pancreatic parameters seems desirable. Since pancreatic hyperenzimemia is related to zinc urinary levels, a future goal could be a personalized zinc dosage based on the patient’s age and weight and urinary zinc levels.
Could the autoimmune phenomenon be predicted in paediatric patients with chronic viral hepatitis?

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**Objectives and Study:** Chronic viral hepatitis is a public health issue both worldwide and in Romania, where the incidence is still high (2-4% for hepatitis B, over 3% for hepatitis C). The autoimmune phenomenon in chronic viral hepatitis is well known today, and it may be clinically overt or serologic. The treatment used for this disease (Interferon) is also known to induce autoimmunity. We aimed to provide a score for the prediction of autoimmunity in paediatric patients with chronic viral hepatitis, which could be useful in monitoring these patients before and during treatment.

**Methods:** We conducted an observational prospective study which included paediatric patients with chronic viral hepatitis B or C who presented to our department from January 2014 to March 2016. We enrolled 114 patients, 92 with chronic viral hepatitis B and 22 with chronic viral hepatitis C. All patients were either naïve or at least 6 month after completing treatment. The autoimmune phenomenon was considered to be present in patients who had positive markers for autoimmunity (positive ANA, LKM1 or ASMA, positive rheumatoid factor, circulating immune complexes, complement abnormalities, positive crioglobulins). We divided the patients in two groups: with and without autoimmune phenomenon, and the groups were compared, considering hematological and biochemical markers. The markers found to be significantly different between the two groups were used to elaborate a score which can predict the presence of the autoimmune phenomenon in patients with chronic viral hepatitis. We used the ROC curve in order to establish the cutoff value for the presence of the autoimmune phenomenon.

**Results:** The autoimmune phenomenon was found in 50% of the enrolled patients. The medium platelet volume as well as serum albumin levels were found to be significantly lower in patients with autoimmune phenomenon (p = 0.022 for both). Significantly higher differences in patients with autoimmune phenomenon were found for ESR (p = 0.007), ALT (p = 0.041), total lipaemia (p = 0.016), LDH (p = 0.042), and serum gamma globulin (p = 0.043). The autoimmune phenomenon was found to be more frequent in patients with high ESR. These patients also had high IgG and high gamma globulin levels. We also found high gamma globulin levels in patients with high ALT. Using the markers found to be different between the two groups, we propose a score of prediction for the autoimmune phenomenon in paediatric patients with chronic viral hepatitis. The score is appreciated to be a fair method to identify the autoimmune phenomenon (area under the curve 0.72, p = 0.000). For a value equal to or above 3 points, the proposed score has a sensitivity of 75% and a specificity of 60%. For a value equal to or above 2 points its sensitivity is 90% but the specificity decreases to 40%.

**Conclusion:** It is important to predict the presence of the autoimmune phenomenon in chronic viral hepatitis especially because these patients often undergo Interferon treatment which may also induce or amplify autoimmunity. The patients at risk may be monitored closely and overt autoimmune phenomena may be avoided. Paediatric patients are at higher risk because the viral infection is present for a longer time and complications are more likely to arise (including the autoimmune phenomenon).

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Effect of sebelipase alfa on survival to 3 years of age and liver function in infants with rapidly progressive Lysosomal Acid Lipase Deficiency: results from two studies

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Objectives and Study Methods: Two studies (VITAL/CL08) are evaluating the safety and efficacy of enzyme replacement with sebelipase alfa (SA) in infants with rapidly progressive lysosomal acid lipase deficiency (LAL-D).

Results: Nineteen infants were enrolled (VITAL, n=9; CL08, n=10). Median age at treatment initiation for VITAL/CL08 was 3.0/2.8 months. As of August 2017, 13 patients continue on study or completed the study; 6 have died. Five are ≥3 years old (all in VITAL) and have been receiving SA for 228-263 weeks. All patients experienced ≥1 serious adverse event (SAE). Seven (37%) had treatment-related SAEs; of these, 5 had infusion-associated reactions (IARs), including 1 patient with an IAR who also had pyrexia. Among patients who did not have an IAR, 1 developed anti-drug antibodies (ADAs), and 1 had pyrexia, pallor, chills, and tachycardia. All SAEs resolved. None discontinued treatment because of tolerability/IARs. Of 17 patients tested for ADAs, 10 had detectable titers; of these, 8 developed neutralizing antibodies, with no apparent effects on safety/efficacy. Median serum alanine aminotransferase levels, 145.0 U/L at baseline (BL, n=9) in VITAL, decreased by 29.6% at week 48 (n=4), 12.5% at week 96 (n=5), and 12.5% at week 144 (n=5); 37 U/L at BL (n=9) in CL08, they showed no change at week 48 (n=7), decreased by 55.2% at week 96 (n=5), and decreased by 90.3% at week 144 (n=2). Serum hemoglobin and albumin levels also improved. Median weight centile, 3.1 (n=8) at BL, increased by 7.5 (n=4) at week 48, 21.8 (n=5) at week 96, and 14.0 (n=5) at week 144 in VITAL; and 0.2 (n=9) at BL in CL08, increased by 27.2 (n=7) at week 48, 45.5 (n=5) at week 96, and 61.7 (n=3) at week 144.

Conclusion: In conclusion, SA is associated with prolonged survival, favorable tolerability, and sustained improvements in disease activity parameters in infants with LAL-D.

Disclosure of interest: S.A. Jones has received grants and travel support for conferences from Alexion Pharmaceuticals, Inc. S. Vijay, S. Fecarotta, and A. Ghosh has received consultancy fees/honoraria from Alexion Pharma GmbH. K. Allen and M. Friedman are employees of and may own stock/options in Alexion Pharmaceuticals, Inc., which sponsored the studies. Editorial assistance was provided by Michael Morren, MBA, RPh of Peloton Advantage, LLC and was funded by Alexion Pharmaceuticals, Inc.
Comparison of diagnostic accuracy of ultrasonography and serum-ALT as screening tests for Non-alcoholic Fatty Liver Disease in children

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Objectives and Study: Ultrasonography (US) and alanine aminotransferase (ALT) are the most commonly used tools for detecting Non-alcoholic Fatty Liver Disease (NAFLD). No head-to-head comparison of these two modalities in children exists. The aim of this study is to compare head-to-head the diagnostic accuracy of ALT and US and their combination for detecting Non-alcoholic Fatty Liver Disease (NAFLD) in children with obesity.

Method: In this prospective cohort study, 99 children (42 male, 57 female), aged 8-18 years (mean age 14.1 ± 2.1 years) with severe obesity (mean BMI z-score 3.3) were included. All patients underwent simultaneous standardized abdominal ultrasonography (US score 1-4) and serum-ALT measurement. The reference standard was steatosis detected using Proton Magnetic Resonance Spectroscopy (¹H-MRS). ROC curve analyses were performed to determine diagnostic performance and to determine optimum screening cut-points aiming for a high specificity (≥80%).

Results: Hepatic steatosis was present in 43.4% of the children. The area under the ROC (AUROC) of ALT and US for the detection of hepatic steatosis was 0.74 (95% CI:0.65-0.83) and 0.70 (95% CI:0.60-0.79), respectively (NS). The sensitivity and specificity for detecting steatosis when using the optimal ALT cut-point (≥ 40 IU/L) was 44% (95% CI:29-60%), and 89% (95% CI:78-96%), respectively. The positive and negative predictive value (PPV, NPV) was 76% (95% CI:58-88%) and 68% (95% CI:61-73%), respectively. The sensitivity for detecting steatosis when using the optimal US steatosis score cut-point (steatosis score ≥ 2) was 51% (95% CI:35-67%), specificity was 79% (95% CI:66-88%), PPV was 65% (95% CI:51-77%) and NPV was 68% (95% CI:60-75%). A combination of ALT, followed by US showed no better accuracy than the individual modalities.

Conclusion: ALT and US have comparable and only moderate diagnostic accuracy for detecting hepatic steatosis in obese children. A stepwise screening strategy combining both methods does not improve the diagnostic accuracy. For practical reasons of costs and availability ALT is the preferred primary screening tool in most settings.

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Characterization of the pediatric population with hepatitis autoimmune in a institution of level IV of Bogota, Colombia - CardionInfantil Foundation Institute of Cardiology of 2011-2017

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Objectives and Study: Autoimmune diseases represent a range of pathologies that require prompt attention due to the morbidity that they entail. Autoimmune hepatitis (AIH) does not escape this group of pathologies, where its timely diagnosis and management define a better prognosis. In many regions of the world its clinical expression is not known and there are no bibliographic reports and take evidence of characterization of other regions. This study was designed with the main objective of characterizing the pediatric population with AIH, taking advantage of the volume of consultation in the pediatric hepatology service of the CardionInfantil Foundation Institute of Cardiology of Bogota, Colombia. This gives us better clarity of the behavior of this type of patients in our region, compare them with other regions and thus we can take better measures for their management and prospective studies in the future.

Materials and methods: An observational, descriptive and retrospective study was carried out. patients diagnosed before age 18 with AIH served by the Department of Gastroenterology and Pediatric Hepatology between January 2011 and May 2017.

Results: We found that 31 patients met the inclusion criteria, 65% were women. With a mean of 9.5 years. According to the AIH type, 83.9% were AIH type 1, 3.2% was type 2 and 12.9% were seronegative. Only one had post-transplant AIH de novo. According to the type of debut, it was acute in 22.6% and chronic in 77.4% of the patients. In 19.3% of the patients, autoimmune sclerosing cholangitis was manifested. 16.1% of the patients required liver transplantation. Of these, 1 was due to fulminant hepatic failure, the others were complications associated with cirrhosis and portal hypertension. With 1-line therapy (prednisolone and azathioprine), 61.2% of the patients had relapse. The main cause was the reduction of corticoid dose in 63.1% of the patients who suffered relapse, followed by non-adherence to treatment in 57.8% of the patients. Of the patients evaluated in this review 2 died, one of them due to chronic liver failure, in which complications were associated and little adherence to medical follow-up, the second patient died of complications infectious diseases associated with post-transplant and immunosuppression.

Conclusion: This first work on the characterization of the pediatric population with AIH in Colombia is of great value, because it has allowed us in a more objective way to know what is the clinical expression and response to the management of our population, taking into account the patients who have been evaluated in this center of reference of pediatric liver diseases of Colombia and this serves as a basis to define what guidelines are taken to improve the opportunity in the diagnosis, monitoring and management of this type of patients. There is a large difference in the type of AIH in our region with developed countries that coincides with reports from other Latin American countries, it was found that AIH type 1 predominates, followed by seronegative AIH, together with the symptoms of chronicity at the debut; also higher relapse rate with first-line therapy; explanation that can be given for not having the measurement of the thiopurine methyltransferase (TMTP) enzyme, in order to reach an adequate dosage of azathioprine.

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Endoscopic retrograde cholangiopancreatography in paediatric population: six-year experience at a tertiary care center in Samsun

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Objectives: Endoscopic retrograde cholangiopancreatography (ERCP) is a combined endoscopic and radiologic procedure used for both diagnostic and more commonly therapeutic interventions within the pancreatic and biliary tree. Experience with ERCP in the paediatric population is limited. The aim of the present study was to evaluate the indications, results and safety of ERCP in paediatric population.

Method: From January 2010 to December 2016, 38 ERCPs were performed to 31 children in Ondokuz Mayıs University Department of Gastroenterology. All procedures were performed by the two gastroenterologists with appropriate training and expertise in ERCP. All patients were placed under deep sedation by an anaesthesiologist and the procedures were performed in the prone position. For all patients, a diagnostic adult duodenoscope was used.

Results: Over the 6-year study period, 38 ERCPs were performed, including 29 (76 %) diagnostic and 9 (24 %) therapeutic procedures on 31 children at our institution. There were 20 (64 %) girls and 11 (36 %) boys aged from 3.58 to 17.9 years. The median age was 13.3 years. The majority of the patients (n = 24) underwent a single procedure, 6 underwent two procedures, 1 underwent three procedures. Of all procedures, 27 (87 %) were for biliary and 11 (13 %) for pancreatic indications. The biliary indications were suspected choledocholithiasis 19 (50 %), post-surgical bile duct injury 4(10.5 %), primary sclerosing cholangitis 2 (5.2 %), parasitic disease (hydatid cyst) 4 (10.5 %), structural and anatomical anomalies 6 (15.7 %). The pancreatic indications included recurrent or chronic pancreatitis 2(5 %) and malignancy 1 (2 %). In all cases, papilla was cannulated. Sphincterotomy in 25 (80.6 %) patients, balloon sweep in 12 (38 %) patients, biliary plastic stent insertion 7 patients (22.5 %), stone extraction in 16 patients (51.6 %), balloon dilatation of biliary strictures in 1 patient (1.5 %) and membrane of cyst hydatid extraction in 3 patients (9.6 %). As a complication after the procedure; 2 (6.4 %) patients developed a 2-fold increase in pancreatic enzymes without symptoms, 1 (3.2 %) with hemobilia and 1 (3,2 %) with mild cholangitis. There was no procedure related mortality.

Conclusion: ERCP is a method that can be used safely in children as well as in adults. Although MRCP and endoscopic USG can be used in place of diagnostic ERCP, the use of ERCP for therapeutic purposes remains important.

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Noninvasive methods for prediction of esophageal varices in paediatric patients with portal hypertension

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Objectives and Study: The development of non-invasive predictive tools to identify patients with esophageal varices (EV) is of major interest, in order to spare them the discomfort and risks of endoscopy and reduce costs. We aimed to evaluate clinical and laboratory parameters as predictors of esophageal varices (EV) in children with portal hypertension.

Method: This study included 100 children older than 6 months of age with intrahepatic portal hypertension, who underwent upper endoscopy for assessment of esophageal varices. Blood tests including full liver function tests and complete blood picture and abdominal ultrasound results were obtained within one month of endoscopy. All patients had no history of bleeding and didn’t take any prior variceal treatment (any type) or variceal bleeding prophylaxis (including nonselective β-blocker use, endoscopic variceal ligation or sclerotherapy). Patients were classified into two groups: with and without EV. Five noninvasive markers were evaluated as potential predictors of EV: (1) spleen size z score, expressed as a standard deviation score relative to normal values for age; (2) platelet count to spleen size z score ratio; (3) clinical prediction rule (CPR) using platelet count, spleen size z score and albumin as variables, \( \left( \frac{0.75 \times \text{platelets}}{\text{spleen z score} + 5} \right) \times 2.5 \times \text{albumin} \); (4) aspartate aminotransferase to platelet ratio index (APRI); and (5) the risk score, calculated as follows: \( 14.2 - 7.1 \times \log_{10} \text{platelets (109/L)} - 4.2 \times \log_{10} \text{bilirubin (mg/dL)} \)

Results: The age ranged between from 6 months to 14 years with median age (IQR) of 3.1 (1.25-5.5) years. Seventy children had EV on first endoscopy. On univariate analysis, spleen size z score and risk score showed significant association with EV. On ROC curve analysis, the best noninvasive predictors of EV were spleen size z score (AUROC 0.77; 95% CI:0.64-0.89), and risk score (AUROC 0.76; 95% CI: 0.62-0.89).

[Receiver operator characteristic curves for the spleen z score and risk score for varices]

The cutoff points were established with the best relationship between sensitivity and specificity for each variable as follows: spleen size z score 2.34 and risk score -2.058. A multivariate logistic regression to detect independent predictors of varices was applied, to reveal that children with spleen size z score >2.34 was 4.8 folds more likely to have EV compared to children with spleen size < 2.34 (95% CI: 1.847-12.580) and the risk score of > -2.058 increases the likelihood of EV (odds ratio 3.23;
95% CI: 1.224-8.525).

**Conclusion:** Children with portal hypertension with spleen size z score > 2.34 and a risk score greater than -2.058 are more likely to have EV. Therefore, these two tests can be helpful in selecting children for endoscopy. Both are non-invasive methods for the assessment of esophageal varices and therefore would not implicate increase in costs.

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Glycosylation disorders are part of liver disease

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Objectives and Study: Congenital disorders of glycosylation (CDG) can lead to liver defect and they constitute an increasing part of the rare diseases. We want to warn hepatologists to consider glycosylation disorders when exploring liver diseases.

Method: We explore several cases with unexplained or atypical severe liver disease including cirrhosis that finally are diagnosed with type II CDG with N and O abnormal glycosylation protein defect.

Results: We present 4 cases with initial diagnosis evoked was: Wilson disease (n=1), Niemann-Pick Disease (n=1) and mitochondrial disorder (n=2). The clinical presentation was for some part atypical and didn’t match with no known evident diagnosis. Finally, we identified for all patients, the same abnormal glycosylation profile and recessive mutation in CCDC115 gene that confirm the CDG disorder.

Conclusion: Hepatologist need to be aware of CDG disorders and to think to explore glycosylation profile when exploring liver diseases.

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Transition of adolescents with pediatric-onset hepatobiliary diseases: systematic review of literature

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Objectives and Study: Long-term prognosis of adolescents with chronic paediatric-onset hepatobiliary diseases (POHD) has dramatically improved in recent decades. Since there is no accepted pathway of care for transition from paediatric (P) to adult (A) hepatologists, we aimed to provide a) a systematic review of literature, and b) an analysis of existing information derived from documents borrowed from other chronic diseases transition experiences.

Method: Out of 657 screened studies published between 1980 and August 2017, identified on Pubmed and Google Scholar by means of keywords (“transition of care” or “health care” and “pediatrics” or “adolescence” or “young adults”), 87 were considered appropriate to be evaluated with the GRADE system (Grading of Recommendations Assessment, Development and Evaluation). Evaluation of international corporate documents included American Academy of Pediatrics, Got transition, ON TRAC (Transitioning Responsibly to Adult Care), Good 2 Go, Stepping Up, National Institute for Health and Care Excellence guidelines.

Results: Existing models of transition have rarely been assessed in randomized controlled trials (RCTs) with outcomes' measurements. Eighty-five per cent of the retrieved studies have a low level of evidence (C/D) according to GRADE system. Consistent with them, transition is generally defined as an active and evolving process that may benefit from a unified approach by P/A staff. Timing of transition should consider the young person's mental and physical development, the socio-economic family circumstances, and the availability of A physicians rather than chronological age only (usually 18 years). Although only 50% of the programs have performed a valid assessment of adolescents readiness for self-empowerment, it is accepted that early training predicts a successful transition. To implement an effective program, a well-coordinated multi-professional team and a integrated and multidisciplinary approach, is requested. Several barriers are reported to impede the transition process. The most relevant for patients/families are poor knowledge on health care system and rights to services, difficulties in identifying the appropriate A specialist, lack of knowledge of their own disease. Lack of a) time for the transition process, b) experienced adult-oriented centres, and c) financial reimbursement appear as critical aspects for P doctors. Adult's physicians consider as significant barriers the scarce training in paediatric diseases and poor communication with paediatricians. A few RCTs have recommended regular web-meetings and suitable technological connections to improve programs effectiveness.
Conclusion: Our systematic review shows that 1. there is still no large unanimity on what constitutes a successful transition for adolescents with paediatric-onset diseases and even less for those with POHD; 2. an evidence-based implementation of an efficient transition policy is still limited by the relative lack of studies resulting in solid data. This preliminary analysis will be used in the making of a specific ESPGHAN/European Association for the Study of the Liver agreed document pointing to remove barriers, influence medical adherence, reduce the prevalence and severity of complications, and improve health-related quality of life for adolescent with POHD.


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Association between (APRI) Index and cirrhosis level, and the value of APRI in prognosis of biliary atresia patients post Kasai procedure

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**Background:** In patients with biliary atresia (BA), early Kasai portoenterostomy (KP) is palliative therapy with hope of restoring bile flow but it cannot stop the progress of hepatic fibrosis. Assessment of hepatic fibrosis is very important predictor of outcome post KP. Although liver biopsy is the gold standard to evaluate liver fibrosis, but it is invasive and has many complications. This study aimed to use APRI for diagnosis of liver fibrosis and prediction of Kasai postoperative prognosis with biliary atresia.

**Objective:** To find association between (APRI) Index and cirrhosis level, and the value of APRI in prognosis of biliary atresia patients post Kasai procedure.

**Method:** A retrospective and prospective descriptive study among 65 BA patients with Kasai operation from 1/2011- 1/2014.

**Results:** A strong association between cirrhosis level (followed Metavir scale) and APRI (p&LT; 0.05). At the severe cirrhosis (F> F2), the area under the ROC curve is 0.798; when APRI was 1.1 the sensitivity is 78.3%, and the specificity is 74.6%. The APRI preoperation among biliary atresia patients still having jaundice after 6 month-operation was higher than the patients whose have had decrease of cholestasis post Kasai procedure (p&LT; 0.05). However the APRI before operation is not associated with survival rates after operation.

**Conclusion:** APRI may be as available tool for assessing liver fibrosis with BA.

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The role of partial external biliary diversion before and after liver transplantation in PFIC-1

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Objectives and Study: Progressive intrahepatic familial cholestasis type 1 (PFIC-1) is an inherited disorder leading to progressive liver damage, severe pruritus and diarrhea. Current treatment options comprise ursodeoxycholic acid (UDCA) treatment, partial or total external / internal biliary diversion and liver transplantation (LTx). Nevertheless, the role and timing of LTx in PFIC-1 remains debated due to persistent no-liver related symptoms, the risk of graft steatosis and overall worse post-transplant survival rates. We present two case reports of male siblings with PFIC-1 who benefited from different treatment.

Both siblings harboured a homozygous mutation in ATP8B1 characteristic for PFIC-1 and both underwent partial external biliary diversion (PEBD) after unsuccessful UDCA treatment at the age of 7 and 5 months respectively. The older brother, after initial improvement of symptoms, developed severe pruritus, cholestasis 9 months after PEBD. He was transplanted from his mother at the age of 16 months. He suffered from severe chronic diarrhea, which started after LTx. Three months after LTx due to abnormal transaminases activity, liver biopsy was performed. There was severe macrovesicular steatosis (95%) with no other changes. Sixteen months after transplantation total biliary diversion was performed, with rapid relief from diarrhea and regression of graft steatosis. Liver biopsy one year after LTx showed 30% of graft steatosis.

In the younger brother we observed persistent severe pruritus and cholestasis (bilirubin > 20 mg/dl, bile acids > 300 ng/ml) after PEBD but we decided to postpone LTx due to lack of living related donor and risk of graft steatosis. Patient remained on UDCA and vitamin supplementation. Eight months after PEBD bilirubin rapidly dropped to 2 mg/dl, bile acids concentration to 65 ng/ml and pruritus disappeared completely.

Conclusions: The good effect of PEBD may be delayed in PFIC-1, thus decision of LTx should be timely made. Total biliary diversion is efficient procedure in case of persistent symptoms after LTx and may reverse graft steatosis in children with PFIC-1.

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Risk and impact of variceal bleed on morbidity and survival in infants and children with cirrhosis

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Objectives and Study: Portal hypertension (PHT) in infants and children is commonly secondary to biliary atresia and portal vein thrombosis. Limited pediatric literature suggests that presence of high risk varices is a strong predictor of variceal bleed. Life threatening complications are seen in one-fifth of cirrhotic children with variceal bleed. The present study was planned with an aim to identify the etiological profile and risk factors associated with variceal bleed in infants and children with and without cirrhosis.

Methods: From Jan'2011 to Oct'2017 all infants and children under 18 years of age with clinical or radiological features of chronic liver disease or PHT were enrolled. Children with asymptomatic elevation of transaminases or chronic hepatitis-B without evidence of chronicity were excluded. The risk of variceal bleed was analyzed in different cohorts of children with liver disease. Outcome of variceal bleed was assessed in terms of morbidity and 90-day mortality.

Results: There were 106 children with variceal bleed, 71% were males. Non-cirrhotic portal hypertension constituted one-third of the cases. The odd's of variceal bleed in the non-cirrhotic cohort was 3.08 (35/69 vs 71/354, 95% CI = 2.03-4.67) in comparison to cirrhotic cohort (p&amp;lt;LT; 0.001), and 1.54 (35/69 vs 23/76, 95% CI = 1.10-2.16, p=0.012) in comparison to biliary atresia. In the cirrhotic cohort, children with autoimmune liver disease had more risk of variceal bleed than those with Wilson disease (19/87 vs 7/88, OR = 2.74, 95% CI = 1.22-6.19, p=0.01). Presence of large varices was found to be a strong predictor of variceal bleed (p&amp;lt;LT; 0.001). 96% of the bleeding episodes were well controlled with a rebleeding rate of 15%. Variceal bleed was related to worsening of ascites, hyponatremia, acute kidney injury, infections, and 90-day mortality in 35%, 33%, 10%, 15% and 24%, respectively. Younger children with biliary atresia had poor tolerance to such bleeding episodes in comparison to those with other etiologies.

Conclusion: Cirrhosis constitutes two-thirds of causes of PHT in children, however the risk of variceal bleed is one-third than non-cirrhotic counterparts. Children with autoimmune hepatitis have more aggressive PHT than those with Wilson disease. Most of these episodes are well controlled by endotherapies, however pose significant morbidity.

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Preliminary experience with high volume Plasmapheresis in pediatric acute liver failure

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Objectives and Study: Acute liver failure in childhood (P-ALF) is a rare condition with high mortality and emergency liver-transplantation (LTx) is often necessary to ensure survival. Management of such critical ill children is complicated and is often extrapolated from studies of adult patients with ALF, inspite that the diagnosis and pathogenesis may differ. In adult patients with acute liver failure, High volume plasmapheresis (HVP) increases transplant-free survival with 13.1%. Only a few small case-report studies on plasmapheresis in P-ALF are available, and there is no data on the safety and clinical effect of HVP in children. The aim of the present study was to investigate safety of HVP in children with P-ALF.

Method: The indication for HVP was severe P-ALF (INR>2, bilirubin>250 µmol/l and/or encephalopathy). HVP was performed with fresh frozen plasma with an exchange ratio of 1:1. The exchanged volume corresponded to 10% of body weight and performed on 3 consecutive days. Daily liver biochemistry, including close measurements after HVP and clinical data were collected.

Results: Sixteen children were enrolled in the study, with 7 children being younger than 31 days. All 16 children completed at least 1 serie of 3 days with HVP. Eight survived with own liver, 5 died, all below 31 days of age at admission. 2 had a successful Liver-Tx, 1 was liver-transplanted but died 5 months later due to graft failure. Among the 6 children who died, time from last plasmapheresis to death was 86 days (mean) with a range from 8-254 days. Procedure related mortality was not suspected in any of the cases. Five were encephalopatic at admission, 2 died and 2 went to Liver-Tx and survived. Four children needed dialysis before HVP due to oliguria, edema and concomitant renal failure. Seven children were ventilated prior to HVP, either due to encephalopathy or they were too small to corporate to HVP. No complication with bleeding during IV access was seen. Two had signs of bacterial infection before the HVP (one with positive culture, one with elevated CRP), none developed clinical or para-clinical signs of infections during HVP. The procedure is potentially associated with delayed alkalosis due to high citrate load (FFP) in the case of liver failure. Tree of the 16 children developed pH>7.55 within the first 12 hours after HVP and were treated with HCL.

Conclusion: In a small group of children no major adverse events of plasmapheresis were seen, and no procedure related mortality. Mortality was high especially among the youngest children. This patient group was highly selected with poor prognosis even prior to enrollment and we might have past the opportunity to treat due to the progression of P-ALF before initiation of HVP.

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Congenital intrahepatic portosystemic shunts in two infants with Trisomy 21

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Congenital porto-systemic shunt (CPSS) are rare conditions detected in 1/30000 children and are divided in two types: intrahepatic and extrahepatic. They are a recognized cause of morbidity affecting different systems and associated with encephalopathy, cholestasis, cardiac and pulmonary complications, as well as the development of malignant and nonmalignant hepatic tumors. Intrahepatic porto-systemic shunts are more rare than extra-hepatic. Patent ductus venosus is a distinct type of intra-hepatic CPSS that less frequently progresses to spontaneous closure.

Association of Trisomy 21 (T21) and CPSS have been only sporadically described in literature. We report two cases of infants with Trisomy 21 (T21) and associated intrahepatic CPSS. The first case is that of a full-term male infant diagnosed with T21, referred to our tertiary center for suspected neonatal infection. He had been born after an uneventful pregnancy and prenatal sonographic findings were normal. He presented with cholestasis, increased levels of aminotransferases (6xN) and hyperammonemia. He was irritable and presented feeding difficulties. An abdominal ultrasound was performed that showed an intrahepatic vascular communication between the main portal vein and the inferior vena cava. The suggested diagnosis was that of a CPSS via patent ductus venosus and the findings were confirmed with abdominal CT-angiography. Other causes of cholestasis (viral, anatomical, drug induced, metabolic) were ruled out and cholestasis also improved. Blood, urine and cerebrospinal fluid remained sterile and antibiotics were discontinued. The infant was put under restricted protein diet (1g/kg) and lactulose, with gradual improvement until normalization of hyperammonemia, irritability and feeding problems. He is now 2months old and his clinical and laboratory state are stable.

The second infant is also a full-term male diagnosed with T21, born without complications after uneventful pregnancy and normal sonographic follow-up. He was admitted in NICU for feeding difficulties. By the time of referral, he had mild cholestasis and normal aminotransferases. The findings on echocardiography showed small atrioventricular septal defect. Abdominal sonography showed mild hepatomegaly and an abnormal communication between the left portal vein and median hepatic vein, consistent with an intrahepatic CPSS. Findings were also confirmed with CT angiography. Ultrasonography follow-up at the age of 1 years old showed persistence of the abnormal portosystemic communication.

CPSS was until now an underdiagnosed condition. The number of CPSS in children has been rising through the last years but they remain rare conditions. Association of T21 has been described but only a few cases have been reported in literature. A registry of these patients should be held to characterize the anatomical patterns of these malformation and define their outcome.

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Assessment of Swallowing function in patients with Wilson's Disease

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Objectives and Study: Wilson's disease (WD) is a complex disorder related to copper metabolism and neurological involvement may lead to severe swallowing disorder in both adult and pediatric patients. The purpose of this study was to investigate swallowing function in patients with WD.

Method: From January 2016 to January 2017, 21 patients with WD were included in the study prospectively. The swallowing function of the patients were imaged with a Videofluoroscopic Swallowing Study (VFSS). Magnetic resonans imaging was performed for patients with neurological presentation.

Results: Of these patients, male female ratio was 1:1.4 and mean age of the patients was 14.9 ± 3.22 years. Their mean age at diagnosis was 8.29±4.23 years. Among 21 patients, 16 (76%) of them present with only hepatic manifestation while 4 of them (19%) present with hepatic and neurological manifestation and only one patient present with only neurological symptom at the time of diagnosis. None of the patients had neither swallowing problems nor remarkable neurological symptoms at the time of diagnosis. Therefore magnetic resonance imaging were found to be abnormal in all patients with neurological symptoms and the most common findings were; symmetrical putaminal signal changes in two patients, symmetrical lesions at putamen and globus pallidus in one patient, hyperintense signal changings in putamen and parietal white matter in one patient. According to the VFSS, only one patient had oral phase dysfunction, and one patient had laryngeal penetration. None of the patients had aspiration during swallowing. Abnormal esophageal body function was detected in 9 (42.9%) patients with WD.

Conclusion: Abnormal esophageal body function was the prominent finding in our study and patients without any symptoms for swallowing dysfunction or neurological involvement may have subclinical swallowing dysfunction that can only be detected with VFSS. Further studies with higher number of patients are needed to reveal the real association between swallowing dysfunction and Wilson’s disease to decrease the disease related morbidity and mortality.

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A rare concurrence of two immune-mediated pathology; autoimmune hepatitis and lichen planus

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Objectives and Study: Autoimmune hepatitis (AIH) is a progressive inflammatory liver disorder characterized by elevated transaminases and immunoglobulin G levels, as well as positivity of non-specific autoantibodies. Lichen planus (LP) is a disease of unknown origin and considered to have an immune-mediated pathology. Association with diseases of immunodysregulation such as alopecia areata, ulcerative colitis, vitiligo, dermatomyositis, morphea, sclerosing cholangitis, thyroiditis, immune thrombocytopenia, celiac disease, and insulin-dependent diabetes previously reported. To the best of our knowledge, association of these two immune-mediated diseases has not been described in childhood before

Results: A previously healthy 16-year-old boy was evaluated for itchy lesions on his knees and lateral parts of lower legs that had been present for 4 months. Dermatological examination showed purple, excorited, lichenified papules and plaques over the knees and lower legs (image 1). White reticular patches are observed on buccal mucosa. A punch biopsy from one of the lesions is performed and histopathological findings were consistent with LP and the lesions were unresponsive to topical treatment. During his follow up, laboratory investigations revealed high transaminase levels; alanine transaminase 203 IU/L and aspartate transaminase 135 IU/L, and the patient was referred for further investigation. Infection serology including hepatitis B, hepatitis C, CMV, and EBV were negative. Metabolic tests, including alpha 1 antitrypsin and ceruloplasmin, were normal. The immunoglobulin G level was normal for his age and autoantibodies for AIH were negative, except for ANA (1/320) positivity. A liver biopsy was performed and showed portal and interface hepatitis, with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils (hematoxylin and eosin), rosette formation, porto-portal bridging and regenerative nodules. Pretreatment autoimmune hepatitis score was 16 (definite diagnosis >15). Oral prednisone 40 mg/day and azathioprine (2 mg/kg/day) were prescribed. Topical clobetasol propionate 0.05% and triamcinolone acetonide 0.1% were prescribed to apply on the skin and oral mucosa, respectively. After two months of follow up, transaminase levels returned to normal (ALT 35 IU/L, AST 31 IU/L). Skin lesions also improved markedly with both oral and topical steroid treatment.

Conclusion: Although both diseases have been frequently reported to be associated with other autoimmune diseases, to the best of our knowledge AIH and LP in the same patient has not been reported previously. We are not sure whether this situation is a coincidence or a real concurrence of two diseases, we need to evaluate more patients with OIH or LP during their follow up to reveal the real association between these disorders.
[Skin lesion of the patient]

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PFIC 4 associated with a new TJP 2 gene mutation - A novel phenotype presenting with intra-hepatic bile duct hypoplasia

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Objectives and Study: Cholestasis in infancy is sometimes secondary to underlying genetic causes. Progressive Familial Intra-hepatic Cholestasis (PFIC) type 4 is a relatively newly described condition with limited clinical information. In this condition, mutations involving the Tight Junction Protein 2 gene (TJP 2) can result in impairment of protein translation and consequent disruption of the tight-junction structure causing severe cholestatic hepatitis with low GGT levels. TJP 2 gene mutations have been associated with a wide spectrum of liver pathology, most commonly resulting in early-onset severe progressive liver disease with associated portal hypertension and more recently, development of hepatocellular carcinoma. We describe a novel phenotype of PFIC type 4 presenting with severe intrahepatic bile duct paucity associated with a previously unreported homozygous TJP 2 gene mutation.

Method: Illustrative case study

Results: A term baby born to non-consanguineous parents presented at 2 months age with progressively increasing jaundice, pale stools and dark urine. An older sibling had died at 5 months of age of an undiagnosed liver disease, having presented similarly. Physical examination confirmed jaundice. There were no dysmorphic features. Firm hepatomegaly as well as splenomegaly was evident with the rest of the systemic examination being unremarkable. Serum bilirubin levels were elevated with low GGT levels (197 micromoles/l; GGT-21 units/l). First-line investigations including plasma amino acids, urine metabolic screen and organic acids, acylcarnitine levels, screening tests for Alpha-1-anti-trypsin deficiency and Galactosemia were negative. Plasma bile acid levels were elevated, making inborn errors of bile acid metabolism unlikely. Although the gall bladder was seen on ultrasound, the rest of the biliary structures were not confidently identifiable. HIDA scan revealed normal hepatic uptake but no excretion. Intra-operative cholangiography revealed a completely normal extra-hepatic biliary tree and porta hepatis. However, there was significant impairment of contrast flow up in to the liver and the intrahepatic biliary tree was only faintly visualized akin to that seen in significant biliary hypoplasia. Wedge liver biopsy revealed significant paucity of intrahepatic bile ducts with associated severe cholestatic and giant-cell hepatitis. Further investigation for genetic disorders in the form of a Next-generation sequencing (NGS) based cholestasis panel revealed homozygosity for a potentially pathogenic TJP 2 gene variant c.898del, that was predicted to result in a frame shift mutation and premature protein termination (p.Arg300Glyfs*11)- likely the primary cause of cholestasis in our patient.

Conclusion: The availability of whole genome and NGS techniques has been an invaluable tool in the management of cholestatic liver disorders as illustrated by our patient with PFIC4 associated intrahepatic duct hypoplasia. We recommend that all children with low GGT cholestasis in whom the aetiology is unclear, be offered genetic screening. Further, children with chronic cholestatic disease and associated bile duct abnormalities or paucity should be offered specific screening for TJP 2 gene mutations.
Non-alcoholic fatty liver disease in obese and non-obese pediatric patients

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Objectives and Study: Nonalcoholic fatty liver disease (NAFLD) is common in obesity, and its incidence is increasing parallel with obesity rates. However, non-obese patients are also increasingly susceptible to NAFLD. This study aimed to compare the clinical characteristics of obese and non-obese pediatric patients with NAFLD.

Method: We retrospectively analyzed 68 NAFLD patients diagnosed at 10–18 years of age between January 2010 and October 2016. Other diseases were excluded in all patients. Obesity was defined as a body mass index (BMI) ≥95th percentile for age and sex or BMI ≥25 kg/m². Laboratory and anthropometric measurements and abdominal ultrasonography were evaluated.

Results: Among the 68 patients, 26 (38.2%) were non-obese. The male-to female ratio was 5.8:1, and the median age at diagnosis was 13 years (range, 10-17 years) in all patients. Non-obese patients had significantly higher triglyceride (223.0 vs. 145.9 mg/dL, p = 0.047) and total cholesterol levels (211.6 vs. 173.2 mg/dL, p = 0.011) than obese patients. In univariate analysis, high-density lipoprotein cholesterol level < 40 mg/dL (HR: 6.5, 95% CI = 2.13-7.10, p = 0.048) and total cholesterol level >200 mg/dL (HR: 5.6, 95% CI = 1.23-15.31, p = 0.038) were associated with increased risk of NAFLD in non-obese patients.

Conclusion: Non-obese patients represent a substantial proportion of pediatric NAFLD cases. Similar to adults, NAFLD should be considered in lean patients, particularly those with metabolic disturbances.
Progressive familial intrahepatic cholestasis type 3 - report of four clinical cases

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Objectives and Study: Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive liver diseases related to mutations in hepatocyte transport proteins genes involved in bile formation and presenting with hepatocellular cholestasis. PFIC type 3 is caused by a genetic defect in the ABCB4 gene, encoding multidrug resistance 3 protein (MDR3). This is related to impaired biliary phospholipid secretion, leading to PFIC. The disease is characterised with high gamma-glutamyltransferase level and heterogeneous clinical presentation. Patients rarely develop cholestatic jaundice in the neonatal period, but rather present in late infancy, childhood, or in young adulthood. The disease spectrum includes transient neonatal cholestasis, progressive cholestasis in late infancy and childhood sometimes leading to cirrhosis and end-stage liver disease, low phospholipid associated cholelithiasis syndrome, intrahepatic cholestasis of pregnancy and drug-induced liver injury.

Method: We report four patients with the diagnosis of progressive familial intrahepatic cholestasis type 3 diagnosed in a tertiary centre.

Results: The first patient is an 8-year-old boy who presents with growth failure since the age of three years and episodes of jaundice and abdominal pain. He was found to have chronic liver disease with advanced hepatic fibrosis. After excluding other causes, he had genetic testing that showed homozygous mutation in ABCB4 gene and the diagnosis was confirmed. We describe two siblings presented at the age of 12 and 14 years with hepatosplenomegaly and raised liver enzymes. One of them had more aggressive disease and developed end-stage liver disease. At present, he is on the waiting list for liver transplantation. One mutation in ABCB4 gene was found but the testing continues. The fourth patient is a 4-year-old girl with advanced liver disease and homozygous mutation in ABCB4 gene. The mutation found in all patients is the same.

Conclusion: PFIC type 3 should be suspected in children with a clinical history of cholestasis of unknown origin after exclusion of other main causes. In some cases, the disease is progressive and may lead to liver transplantation.
Clinical picture and biochemical findings in the course of late onset lysosomal acid lipase deficiency in Polish patients

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Objectives and Study: Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal lipid storage disorder characterized by the accumulation of cholesteryl esters and triglycerides. Depending on the residual enzyme activity, LAL-D results in an early-onset, severe and lethal phenotype, known as Wolman disease, or a late-onset, attenuated phenotype, cholesteryl ester storage disease. The aim of our study is to present the natural history of late-onset LAL-D, focusing on the first noted abnormalities in Polish patients.

Method: This is a long-term (over 30 years) observational, one-centre study of patients with late-onset LAL-D. The study population consists of 18 patients of Polish origin. Diagnoses were based on a deficient LAL activity in leukocytes and the LIPA gene mutations (in the majority of cases). Liver biopsy and thin-layer chromatography of total liver lipids were done in 14 out of 18 cases. A retrospective chart review of patients’ medical records concerning the first presented signs and symptoms, as well as biochemical, histological and molecular data were collected.

Results: Thirteen (72.2%) patients had no complaints and all the patients had normal psychomotor development. The mean age at which the first symptoms were reported by a physician was 4 years and 6 months with the age range 0.5-13 years. A mild hepatomegaly was the most common initial abnormality observed in 12 (66.7%) patients, while 6 (33.3%) of patients had also splenomegaly. Seven (38.9%) patients were noted to have mildly to moderately elevated serum transaminases. At the time of first hospitalization in our clinic, all (n = 18) the patients had dyslipidemia (in the form of elevated serum total and LDL cholesterol, high triglycerides and low HDL cholesterol) and 15 (83.3%) patients presented with elevated serum transaminases.

Liver biopsy was performed in 14 out of all 18 patients at the mean age of 6 years and 11 months. Lipid storage process was reported in 9 (69.2%) patients while the liver steatosis in 4 (28.6%) patients. The evidence of fibrosis was reported in 7 (53.8%) patients and cirrhosis in 3 (21.4%) patients. The mean age at the time of CESD diagnosis was 7 years and 5 months.

The molecular data were available in 9 (52.9%) patients. All the patients from our cohort were carriers for the mutation c.894G>A in the LIPA gene. Among them, 4 (44.4%) patients were homozygous for this mutation. The other variants were c.386A>C (2 patients were heterozygotes), c.538+5G>A (2 patients were heterozygotes) and c.309C>A (heterozygous in 1 patient).

Conclusion: Hepatomegaly constitutes the most common reported symptom of late-onset LAL-D, which could persist as the only symptom for years. In general, in a case of the coexistence of hepatomegaly, elevated serum transaminases and type IIb dyslipidemia, we should always think about possible late onset LAL-D diagnosis. Taking into consideration that more than a half of our studied patients had no complaints we would like to emphasize that late-onset LAL-D might have a relatively mild phenotype. The latter could be related to the presence of c.894G>A mutation on at least one allele of the LIPA gene. The presence of this mutation alleviates the clinical phenotype. Thus, the disease may be overlooked leading to delayed or misdiagnosis.

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Handgrip strength among Korean adolescents with suspected non-alcoholic fatty liver disease in 2014-2015

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**Objectives and Study:** The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide in both adults and adolescents. Sarcopenia is known to be associated with NAFLD. Furthermore, measuring handgrip strength is a useful method to evaluate sarcopenia. This study aimed to define the correlation between handgrip strength and NAFLD, based on data from the Korea National Health and Nutrition Examination Survey (KNHANES).

**Method:** Data of 1,057 adolescents (577 boys; 480 girls; age, 10-18 years) who participated in the KNHANES in 2014 and 2015 were obtained. The highest handgrip strength was recorded in bilateral hands. The definition of NAFLD was overweight status (≥85th percentile for body mass index for age and sex) and elevated alanine aminotransferase (ALT) levels (>24.2 U/L for boys and >18.1 U/L for girls).

**Results:** Handgrip strength was higher in participants suspected to have NAFLD. Handgrip strength in participants without NAFLD and those with NAFLD were 28.3±0.4 and 33.5±1.5 kg, respectively (P=0.001). Conversely, when we incorporated handgrip strength into a ratio of the participants' weight and BMI, the handgrip-to-weight and handgrip-to-BMI ratios in participants with NAFLD were lower than those of participants without NAFLD (42.2±1.3 vs. 51.5±0.5 and 117.3±4.6 vs. 136.5±1, respectively; (P&LT; 0.001)). Among participants with NAFLD, handgrip-to-weight ratio was 44.3±1.3 in participants without fibrosis, and 35.9±1.9 in participants with fibrosis (P&LT; 0.001).

**Conclusion:** Handgrip strength is a useful tool to evaluate sarcopenia. Handgrip-to-weight and handgrip-to-BMI ratios were decreased in participants with NAFLD. Further evaluation is needed to clarify the relationship between NAFLD and handgrip strength in adolescents.

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Oxysterols in pediatric acute liver failure with hepatic encephalopathy: a pilot study

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Objectives and Study: Oxysterols are oxygenated derivatives of cholesterol. There have been some reports of oxysterols in adults with hepatic or neurological disorders but few reports in children. Acute liver failure with hepatic encephalopathy (ALF) is a poor prognostic disease which causes severe damages of liver and brain. The aim of this pilot study is to clarify whether oxysterols are a useful biomarker in pediatric ALF.

Method: Subjects were 12 children including 3 ALF patients, 3 liver disease controls (LDC, chronic hepatitis) and 6 healthy controls (HC). LDC and HC were age-matched children with ALF patients. Seven kinds of oxysterols including 4β-OH-cholesterol, 20α-OH-cholesterol, 22(R)-OH-cholesterol, 22(S)-OH-cholesterol, 24(S)-OH-cholesterol, 25-OH-cholesterol, and 27-OH-cholesterol in their serum and urine were analyzed using liquid chromatography-mass spectrometry.

Results: Urinary 4β-OH-cholesterol, 22(R)-OH-cholesterol, 24(S)-OH-cholesterol, and 25-OH-cholesterol in children with ALF were significantly elevated than LDC (P&LT; 0.05, 0.01, 0.001, and 0.001) and HC (P&LT; 0.05, 0.01, 0.001, and 0.001), respectively.

Conclusion: Urinary oxysterols may be a useful biomarker in pediatric acute liver failure with hepatic encephalopathy.

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The frequency of lysosomal acid lipase deficiency in children with unexplained transaminase elevation and chronic liver disease in Turkey

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Objectives and Study: Lysosomal acid lipase (LAL) deficiency (D) in children and adults affects the liver among other organ systems involved in lipid metabolism. Pediatric and adult patients with LAL-D are often misdiagnosed, because symptoms may be nonspecific. The aim of this prospective, multicenter and cross-sectional study is to investigate the frequency of LAL-D in children with unexplained transaminase elevation and/or chronic liver disease and to identify demographic and clinical features.

Method: Patients aged 3 months to 18 years at the time of enrolment who had unexplained transaminase elevation (serum ALT levels > 1.5 times the upper limit of normal) for >3 months and/or unexplained hepatomegaly or hepatosplenomegaly, obesity-unrelated hepatosteatosis, biopsy-proven cryptogenic fibrosis and cirrhosis and liver transplantation (LT) for cryptogenic cirrhosis were enrolled in 41 centers in Turkey, between January 2015 and January 2017 (ClinicalTrials.gov Identifier NCT02372513). A web-based electronic data collection system was used; including demographics, complete family and medical history, physical examination, laboratory findings and LAL enzyme activity levels. LAL enzyme activity was measured from Dry Blood Spots (DBS) samples in the reference laboratory [NHS Greater Glasgow & Clyde Biochemistry Department, Glasgow, UK]. A LAL enzyme level < 0.02 nmol/punch/h was classified as LAL enzyme deficiency, > 0.37 nmol/punch/h was classified as normal and 0.02-0.37 nmol/punch/h was considered as an intermediate activity. A second DBS sample was obtained from patients with intermediate LAL enzyme activity. The diagnosis of LAL-D was based on LAL enzyme activity level.

Results: A total of 810 patients (60% male; mean age 6.9 ±5.7 years) were enrolled. The median time interval between symptom onset and enrollment of the study was 16.7 months (range: 3-210 months). The causes of enrollment were unexplained transaminase elevation in 503 patients (62%), unexplained hepatomegaly in 364 (45%), obesity- unrelated hepatosteatosis in 212 (26%), cryptogenic fibrosis and cirrhosis in 364 (45%), obesity- unrelated hepatosteatosis in 212 (26%), cryptogenic fibrosis and cirrhosis in 53 (6%) and LT for cryptogenic cirrhosis in 7 (> 1%). Consanguinity was noted in 27% of the patients.

LAL-D was identified in 2 siblings (0.25%) (15 year-old boy and 6 year-old girl) born from unrelated parents. They had growth failure, hyperlipidemia, hepatosteatosis on abdominal ultrasound imaging and a family history for hyperlipidemia. The girl had also elevated transaminase levels. A liver biopsy was performed in the boy who revealed microvesicular steatosis, portal inflammation and bridging fibrosis.

For 76 patients who had intermediate LAL enzyme activity at the first measurement, the results of a second measurement showed a significant increase in LAL enzyme activity compared with the first measurement. Of these 76 patients, 38 had normal enzyme activity on second measurement whereas for 38, the LAL enzyme activity in the DBS test remained at intermediate level.
<table>
<thead>
<tr>
<th></th>
<th>LAL enzyme activity n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>634 (78.3)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>174 (21.4)</td>
</tr>
<tr>
<td>Deficient</td>
<td>2 (0.25)</td>
</tr>
</tbody>
</table>

[LAL enzyme activity levels (n=810)]

**Conclusion:** Our results indicate that the frequency of LAL-D is 1 in 405 among children in Turkey with unexplained, transaminase elevation and/or chronic liver disease.

**Disclosure of interest:** This investigator sponsored research supported by Alexion Pharmaceuticals Inc. Also, Alexion Pharmaceuticals Inc. performed a courtesy review of the abstract before submission.

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The effect of light from phototherapy on total micro-bilirubin values in vitro

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Objectives and Study: To study the effect of light from phototherapy on total micro-bilirubin values in vitro.

Method: 414 capillary blood samples were collected with micro-tubes from jaundiced newborn infants at the nursery of Veterans General Hospital-Taipei. Samples were divided into 2 groups: 1. Phototherapy group - 199 samples were placed on infant cribs and irradiated with blue fluorescent light from phototherapy light source in a distance 150 cm apart(spectral irradiance 425-475 nm=4 µwatt/cm²/nm); 2. Dark group - 215 samples were placed in the dark. Total bilirubin values were checked with spectrophotometry at 0, 2, 4, 6, 24 and 48 hours after placing in different environments. The mean values obtained in 2 groups were analyzed with 2-way ANOVA with repeated measurement and Duncan's multiple range test.

Results: There were significant decreases in bilirubin values of the phototherapy group beginning at 2 hours (p< 0.05), and there was no change of bilirubin values in the dark group.

<table>
<thead>
<tr>
<th>Time(hours)</th>
<th>Phototherapy group(mg/dL)</th>
<th>Dark group(mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.92±2.51</td>
<td>9.23±2.74</td>
</tr>
<tr>
<td>2</td>
<td>*7.07±2.21</td>
<td>9.25±2.73</td>
</tr>
<tr>
<td>4</td>
<td>*6.25±2.02</td>
<td>9.24±2.77</td>
</tr>
<tr>
<td>6</td>
<td>*5.66±1.84</td>
<td>9.20±2.78</td>
</tr>
<tr>
<td>12</td>
<td>*2.04±1.04</td>
<td>9.08±2.77</td>
</tr>
<tr>
<td>24</td>
<td>*0.49±0.41</td>
<td>8.73±2.76</td>
</tr>
</tbody>
</table>

[ Mean values of total micro-bilirubin(*p<0.05) ]

Conclusion: If blood samples for micro-bilirubin values are exposed to light from phototherapy, errors may occur within 2 hours. In order to obtain accurate micro-bilirubin values, the light of phototherapy should be turned off before blood sampling has been started. Micro-bilirubin values of blood samples may maintain steady at least 48 hours if they are placed in dark environment.
Paediatric acute liver failure in a multi-ethnic Southeast Asian cohort at a single tertiary centre

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Objectives and Study: Paediatric acute liver failure (PALF) is a rare, rapidly progressive condition with significant morbidity and mortality. Apart from timely and appropriate intervention, the age of onset and aetiologies of PALF are important factors that may influence outcome. This study aimed to evaluate the characteristics of PALF patients to determine factors influencing survival rate at a single, tertiary paediatric centre in Singapore.

Method: Retrospective single centre review of patients under 18 years diagnosed with PALF over a 10-year period from 2007-2017. Paediatric Acute Liver Failure was defined as biochemical evidence of acute liver injury in the absence of pre-existing liver disease; coagulopathy not corrected by intravenous Vitamin K, i.e. prothrombin time (PT) > 20 seconds and International Normalized Ratio (INR) > 2.0 without encephalopathy or PT > 15 seconds and INR > 1.5 seconds with encephalopathy.

Results: Twenty-six children (20 male) were identified during the study period. Median age at diagnosis was 10 months (range 0.2-156 months), with 54% presenting under the age of 1 year. Majority (62%) were of Chinese ethnicity. The most common aetiology for PALF in children less than 12 months of age was infectious (50%), followed by inborn metabolic disorders (36%), and indeterminate (7.1%). All patients with metabolic aetiology presented at less than 3 months of age. In contrast, the aetiology of PALF was indeterminate in the majority of children older than 12 months of age (58%), while specific causes were identified as infectious in 25%, Wilson’s disease in 8% and drug induced liver injury in 8%. Viral hepatitis A and B, and autoimmune liver disease were not identified as causes of PALF in our population. The overall survival (OS) rate is 46% and transplant-free survival (TFS) rate is 31%. Eight patients were listed for liver transplantation (LT), 5 underwent LT but 3 died before LT surgery. LT was contraindicated in 10 children due to ongoing sepsis and/or multi-organ involvement. Post-transplant survival is 80%. One patient who underwent LT died 3 years post-transplant from chronic graft failure. Overall mortality was significantly higher in children aged less than 12 months as compared to the older group (64% versus 33%, p=0.03). Metabolic causes for PALF were most likely to result in death or require LT (83%), while indeterminate and infectious aetiologies were associated with higher rate of recovery without LT (38% and 30% respectively). The need for invasive ventilator support (OR 14.0; 95CI: 1.39-141.5, p=0.025) was significantly associated with LT or death, while no association was observed between severity of derangement in liver and renal biochemical parameters and OS and TFS rates.

Conclusion: PALF is associated with poor survival across all aetiologic groups, however a significantly higher mortality rate is seen in infants less than 12 months old, and in those with metabolic aetiology. Survival rate for patients who underwent LT was 80%, hence timely access and assessment for LT at a paediatric transplant facility may improve overall survival in children with PALF.
[Outcome of 26 children with paediatric acute liver failure admitted to a tertiary paediatric unit in]

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Anthropometric index as a screening marker for nonalcoholic fatty liver disease in children

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Objectives and Study: To assess the role of anthropometric parameters and their ratio in the prediction of nonalcoholic fatty liver disease (NAFLD) in children. The study included 90 patients aged 5 to 17, boys - 54 (60%), girls - 36 (40%). The average age of patients was (12.08 ± 2.71) years. All patients and their parents had given their agreement to participation in the study.

Method: The presence and degree of hepatic steatosis were determined by transient elastography using «FibroScan®502 touch» with the measurement of controlled attenuation parameter (CAP) and liver stiffness (LSM). We measured weight, height, waist circumference (WC) and hip circumference (HC). Univariate binary logistic regression was used to identify variables associated with NAFLD. A model combining waist-to-hip ratio, age, WC to 90 percentile of WC value ratio was used with calculation of anthropometric index (AI). The discriminatory performance of AI in the diagnosis of NAFLD was evaluated by receiver operating characteristic analysis.

Results: The prevalence of NAFLD among obese children was 56.25%. The optimal cutoff points of AI was 1.64 (sensitivity 0.82, specificity 0.77, Youden’s index 0.59). We found that area under the curves for AI was 0.83; 95% CI 0.70-0.92. AI revealed a positive correlation with the CAP and LSM (r=0.58; r=0.26; respectively, p&LT; 0.05).

Conclusion: Thus, the proposed calculation marker can be used for non-invasive diagnosis of liver steatosis in children at stages of outpatient and non-specialized care reducing the time of examination and making possible with a high level of sensitivity and specificity to identify a group of patients requiring a more detailed examination to confirm the diagnosis of NAFLD.

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Transjugular liver biopsy in children and adolescents

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Objectives and Study: Transjugular liver biopsy (TJLB) is widely used in adult patients when percutaneous liver biopsy is contraindicated. Our aim was to evaluate the safety, efficacy and utility of transjugular liver biopsy in pediatric patients who had significant coagulopathy or ascites precluding liver biopsy.

Method: Fifteen children and adolescents (8 male) aged 8 to 18 years from January 2016 to November 2017 underwent the procedure (TJLB) under general anaesthesia (12) or intravenous sedation (3). Standard percutaneous liver biopsy was contraindicated because of significantly elevated PT/INR (>15.5/1.5) in 11 (73.3%) patients and thrombocytopenia (<60000/dl) in 9 (60%) patients. Among 15 children, 6 (40%) patients had actually severe derangement in both INR and platelet count. Clinically significant ascites was also present in 6 (40%) patients. Initial provisional diagnoses before TJLB were autoimmune hepatitis (6), Wilson's disease (2), portal hypertension under evaluation (2), chronic liver disease with hypersplenism (2), HBV related cirrhosis (2) and refractory ascites of unknown etiology (1).

Results: Adequate biopsy samples for a definitive diagnosis were obtained in 14/15 patients (technical success rate 93.3%). No major or minor complications were seen. A new diagnosis was established in 4 (26.6%) cases (chronic Budd Chiari syndrome, congestive heaptopathy, non cirrhotic portal fibrosis and normal liver). Another 9 (60%) cases revealed the histopathology of initial suspected etiology (6 AIH, 2 Wilson’s, 1 Chronic hepatitis B) and helped us to start definitive treatment accordingly. In one case, admitted with acute on chronic liver disease, definitive diagnosis could not be reached due to acute hepatitis A virus induced cytopathic changes in the background of chronic hepatitis.

Conclusion: Despite the limited number of patients in our study, transjugular liver biopsy appears to be a safe and effective method and also useful modality for etiological diagnosis and treatment decision in pediatric patients, where percutaneous biopsy is contraindicated.

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Introduction: Wilson disease is an autosomal recessive defect of cellular copper export. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues leading to a multitude of signs and symptoms that reflect multiorganic impairment. Worldwide, the prevalence of Wilson disease is approximately 1 per 30,000 individuals. The genetic defect, localized to arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver. The diagnosis is established by the combination of serum ceruloplasmin level, urinary copper excretion, presence of Kayser-Fleischer rings, and hepatic copper content when biopsy is required. The goldstandard of therapy for Wilson disease is pharmacologic treatment with chelating agents such as D-penicillamine and trientine. D-Penicillamine is associated with multiple side effects leading up to approximately 5 percent of patients to discontinue therapy. In association with D-Penicillamine therapy, skin changes have been described including elastosis perforans serpinginosa. It is estimated that 1 percent of patients treated for decades with D-Penicillamine will develop elastosis perforans serpinginosa.

Description: An 16-years old adolescent girl, with the diagnosis of Wilson disease since 5 years old, treated with D-penicillamine for the last 11 years, within good medication compliance, reported the sudden onset of cutaneous eruption on the anterior region of the neck, with multiple erythematous macules, 0.2 to 0.5 cm in diameter, and associated pruritus. At that time, the daily dose of D-Penicillamine was 1200 mg and pyridoxine 300 mg once a week. She denied any other medications or any other symptoms. The patient consulted her paediatric gastroenterolog promptly who assumed to be a side effect of D-Penicillamine treatment and was asked for Dermatology consultant. Dermatologist examined the patient, also agreed with the first diagnostic hypothesis and performed a cutaneous biopsy of the lesion. The pathological anatomy report confirms that it was “elastosis perforans serpinginosa which could be due to D-penicillamine treatment”. The previous therapy was changed to oral zinc, a daily dose of 150 mg, with satisfied results. Now she is a young adult with Wilson disease stabilized.

Conclusion: Despite being rare, elastosis perforans serpinginosa secondary to D-Penicillamine therapy should be considered when cutaneous eruption sudden onset in a patient treated with this drug. After the recognition of this condition, it is crucial to change the therapy and then refer the patient to dermatology consultant. The early diagnosis is crucial to dictate the best prognosis which usually is favorable.

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Liver stiffness in 196 healthy children, comparing two shear wave elastographic systems and transient elastography

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Objectives and Study: Ultrasound elastography is a non-invasive method assessing liver stiffness (LS) as an estimation of fibrosis. However, the various elastography systems may yield different values for any given liver reflecting technological differences, hence system-specific reference values are warranted. We aimed to establish reference values for LS in a population of healthy children aged 4-17 years, for point shear wave elastography (pSWE, Samsung RS80A) and 2D shear wave elastography (2D-SWE, GE Logiq E9). Furthermore, we aimed to compare median LS for the two modalities and, in a subset, we aimed to compare pSWE and 2D-SWE with transient elastography (TE, Fibroscan).

Method: 196 children aged 4-17 years were included and divided into 4 age groups: 4-7 years (N=44), 8-11 years (N=55), 12-14 years (N=46) and 15-17 years (N=51). Subjects were fasting 3 hours prior to the investigation. Their medical history was recorded and all children were evaluated clinically by a paediatrician. Height, weight and waist circumference were recorded. B-mode ultrasound scanning was performed to exclude signs of liver pathology. pSWE and 2D-SWE were performed in all children. TE was performed in a subset from the older age groups (n=72). In a subset (N=25), two observers individually obtained LS measurements with pSWE and 2D-SWE for inter-observer reliability testing. Results were given as the median of 10 valid acquisitions and measurements were excluded if interquartile range (IQR)/median ≥30% or (for TE) a success rate &LT; 60%.

Results: Feasibility was excellent for all systems, with failure rates of 0, 1.5 and 6.9% for 2D-SWE, pSWE and TE, respectively. Median LS was significantly higher for pSWE (4.22±0.81 kPa [range 2.8 - 7.1]) compared to 2D-SWE (3.62±1.14 kPa [2.0 - 7.7]; P=0.001). For observer 2, these values were 4.16±0.85 kPa and 3.78±0.96 kPa, respectively. Inter-observer reliability was excellent, displaying no significant difference between observers (P=0.75 and P=0.65 for 2D-SWE and pSWE, respectively). Median LS for TE was 4.20±1.25 kPa, showing similar values to pSWE (P=0.903) and significantly higher values than 2D-SWE (P< 0.001). Both for pSWE and 2D-SWE, median LS increased significantly with age; for 2D-SWE the three oldest age groups were all individually significantly higher than the youngest age group (P< 0.001, P< 0.001 and P=0.001 for group 4, 3 and 2, respectively), for pSWE p-values were P=0.02, P< 0.001 and P=0.11, for group 4, 3 and 2, respectively.

Conclusion: All elastography methods were feasible in children, with good intra- and interobserver reliability. 2D-SWE (GE) yielded significantly lower liver stiffness values compared to pSWE and TE. Measurements in older children were significantly higher than in younger children for both 2D-SWE and pSWE.

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Metabolic liver diseases presenting with Neonatal Cholestasis: a series of 13 cases

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Background and Aim: Cholestatic jaundice in early infancy is a complex diagnostic issue. Metabolic liver diseases (excluding alpha-1-antitrypsin), although individually rare, represent approximately 10-20% of the cases.

The aim of this study was to review the clinical phenotype of Metabolic Liver Diseases (MLD) presenting with Neonatal Cholestasis (NC), highlighting the need to consider them on the differential diagnosis of the cholestatic infant.

Methods: We retrospectively analyzed a series of 120 patients with NC, referred to a tertiary center during a 30-year period (1987-2017), from which we identified a cohort of 16 patients with MLD. NC was defined as conjugated hyperbilirubinemia of more than 1 mg/dl occurring in the newborn or infants aged less than 4 months. Liver failure was diagnosed according to Pediatric Acute Liver Failure (PALF) study group criteria. Transient neonatal cholestasis was considered when spontaneous resolution occurred before 6 months old. All patients underwent extensive workup to diagnose infectious, structural, metabolic, endocrine, infiltrative, and genetic causes. We excluded patients with the presence of other concomitant diagnosis or known risk factors for developing neonatal cholestasis. Patients with NC in the context of MLD were categorized into 3 sub-groups, according to clinical and analytical evaluation: 1) NC with liver failure; 2) NC evolving progressing to chronic liver disease, and 3) Transient NC.

Results: We identified 16 infants with MLD and NC. From these, three patients - Infantile Refsum (1) and peroxisomal disease (2)- were excluded because of insufficient clinical and analytical data. Five patients presented with NC and liver failure: Tyrosinemia type I (1), Galactosemia (3), mtDNA depletion syndrome (1). The patient with Tyrosinemia type I underwent liver transplantation; those with galactosemia are stable under diet measures; the patient 5 died at the age of 8 months old. Four patients had NC evolving with chronic liver disease: Argininemia (2); Mitochondrial cytopathy (1); Congenital Disorder of Glycosylation Type Ia (1). Three patients presented as transient NC: Niemann-Pick type C (2) and Citrullinemia (1).
Conclusion: MLD may present as NC, assuming very different liver-disease phenotypes. We particularly emphasize that some inborn errors of metabolism may present as transient neonatal cholestasis. In those cases, MLD should be included in the diagnostic workup, so that they are not missed.

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Autoimmune hepatitis type 2, a series of 41 patients

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Objectives and Study: To describe Type 2 Autoimmune Hepatitis (AIH-2) observed in a referral centre.

Method: The files of children with AIH-2 were reviewed.

Results: From 1985 to 2017, 41 LKMpos &1 LC1pos AIH were observed. Females were 34 (83%). Age ranged 0.6-16 years; 34% & LT; 3 years, 49% 3 to 10 years old, and 17% adolescent. Liver disease (LD) was detected due to liver symptoms in 46%, unspecific complaints in 39% and check-ups in 14.6%. HBV, HCV and HAV serology was negative. Associated AI diseases were found in 11 (27%): 3 coeliac disease, 2 diabetes, 1 each: psoriasis, scleroderma, hypothyroidism, atrophic gastritis+colitis, thrombopenia, IgA deficiency. Other autoAb (thyroid, GPC) were detected in 4. The series included a family (2 girls, 1 boy) with AIH-2 detected years apart upon jaundice. 1st-degree relatives of 8 other cases had AI disease. LD at presentation was classified as acute liver failure (ALF) in 17%, LD with jaundice in 24.3% and LD without jaundice in 58.5%.

1) ALF group (n=7): Age ranged 7-25 months. All developed encephalopathy. Laboratory showed ALT 1435± 598 U/L, Total bilirubin 20.2±6.3 mg/dL, Prothrombin activity 22±7%. IgG ranged: 991-1540 mg/dL. LKM titer was 1:160-1:5120. No other AI disease was present in patients or family. All received methylprednisolone (MPred) 2 mg/kg, with cyclosporine (n=1) and Azathioprine (Aza) (n=3). Outcome was:
   a) Two (28.5%) recovered from failure (2nd & 3rd week) and achieved remission (6th & 9th month). LKM disappeared. Biopsy at 3rd month in 1 showed mild fibrosis. Follow up (FU) (16 & 20 yrs) showed normal function on MPred (2-4 mg/day), plus Aza 1mg/Kg in 1. One had dysfunction due to non-compliance at age 19 yrs.
   b) Five (71.4%) underwent urgent liver transplantation (LT); explants showed massive/submassive necrosis.

2) LD with jaundice (n=10). Age was 10±4.2 yrs, 50% were adolescent. Bilirubin has normalized in 2 at referral. Mean ALT = 1508 (242-3556) U/L, IgG 2424±915. Coagulation was abnormal in 5. Outcome with MPred-Aza was:
   a) Remission in 7 (70%) (1 with protracted course, 4 with relapses). At last FU ALT was 32±18 U/L. LKM persisted in 5.
   b) In 3 patients, all showing coagulopathy and splenomegaly at onset, LD did not improve and LT was performed (0.5-2nd month). All explants showed cirrhosis.

3) LD without jaundice (n=24): age was 5.4±3.4, just 8% adolescent. They came with: decompensated LD after 6 years treated (n=1), detection of splenomegaly & thrombopenia (n=2), or abnormal ALT without signs of advanced disease (n=21). ALT was 391±385 IgG 1457±535 mg/dL. Coagulation was abnormal in 2. Outcome with MPred+Aza was:
   a) Remission in 21 patients (87.5%). At last FU ALT was 17±7 U/L and IgG were normal in all, 9 remained LKM/LC1 positive, dose was Mpred 1-6 mg/day (n=18) and/or Aza 1mg/kg (n=21).
   b) LT performed or indicated in 3 cirrhotic patients, 1 immediate, and 2 after 2&4 years in biochemical remission but severe portal hypertension.

Conclusion: AIH-2 presented with a wide spectrum of LD. Children & LT; 3 yrs old accounted 34% and had either ALF (50%) or not severe LD (50%). In chronic LD, cirrhosis was found in 24%.

Presentation with jaundice had significant differences (older age, higher ALT & IgG, less perfect parameters of remission) compared with children without jaundice.
Immune response and anamnestic immune response in children after a 4-dose primary hepatitis B vaccination

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Tunisia is an intermediate hepatitis B virus (HBV) endemic country. The vaccination was introduced in 1995 including four doses with a first birth dose. Decreasing the level of antibodies against hepatitis B surface antigen (anti-HBs) over the time can be alarming.

Objectives and Study: We aim to determine the immune response for children figuring between 7 months to 6 years of age and to evaluate the anamnestic immune response

Method: We conducted a cross-sectional prospective study from June 2016 to June 2017 (n=180), based on voluntary participation following an explanation of the goals of the study. Antibody to HBV surface antigen (anti-HBs) was determined using electro-chemiluminescence micro-particle immunoassay (ECLIA).

Results: The mean age at the time of enrollment for the study was 33 ±14.8 months. The seroprotection rate was 77.2%. Protective responses to the HBV vaccine as measured by levels of anti-HBs differed significantly between the different age groups (p=0.002). The significant predicting variable for having no seroprotective level was older age. Children with anti-HBs levels <10 UI/L were offered an additional dose of HBV vaccine. Anamnestic response one month after the challenge dose was observed in 100% of subjects. The probability of developing a high antibody response following the booster increased in conjunction with an increased pre-booster antibody level.

Conclusion: The response to a booster dose suggests persistence of immune memory in almost all those vaccinated. Although a booster dose increases substantially anti-HBs titer, the clinical relevance of such an increase remains unknown.

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Objectives and Study: Wilson's disease is an autosomal recessive disorder of copper metabolism. The underlying cause is a mutation of ATP7B gene located on 13 chromosome. There are over 800 hundred mutations described to evoke WD. The aim of this study was to analyze the frequency of particular ATP7B mutations in relative big cohort of Polish pediatric population with WD.

Methods: 151 Polish children with WD diagnosed according to Ferenci scoring system had molecular analysis of ATP7B gene by direct sequencing of exons 1-21 performed.

Results: 284 mutated alleles with 41 different mutations were identified among investigated samples. In 18 children only one mutated allele was found. 189 out of 284 (66,5%) was p.H1069Q, 26 (9,1%) was p.A1135fs, 10 (3,5%) was p.Q1351X and 5 (1,8%) - W779X and p.R969Q (each). 3 further mutations (p.N1270S, p.G1158fs, p.E507fs) were found in 3 alleles (1,1%), 8 in 2 alleles and 24 in one allele each. 59 patients were homozygous for p.H1069Q mutation, 4 for p.A1135fs and 1 for Q1351X, R778G and G1158fs (each). Using the three most common mutations 86 of 151 (57%) children were diagnosed with two mutations in both alleles.

Conclusions: p.H1069Q is the most common mutation in Polish pediatric population with WD (with frequency up to 66%). Over ¾ of all mutations are the three most common: p.H1069Q, p.A1135fs, p.Q1351X and using those mutations allow diagnosis in more than half of the patients. 44% Polish children with WD are homozygous.

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Objectives and Study: Wilson’s disease is an autosomal recessive disorder of copper metabolism. The underlying cause is a mutation of ATP7B gene located on 13 chromosome. There are over 800 hundred mutations described to evoke WD and mutations within ATP7B are very heterogeneous. They can be divided into missense, nonsense and frameshift ones. The two last ones are regarded as severe because of more substantial changes in ATP7B protein. The aim of this study was to compare phenotypic expression of various types of ATP7B mutations in Polish children with WD.

Methods: Among 151 patients, 98 children had two missense alleles or only one missense allele detected without second mutation (mild group) and 53 remaining had at least one frameshift or nonsense mutation (severe group). The demographic (age at onset and age at diagnosis), clinical (hepatomegaly, splenomegaly, ascites, jaundice), laboratory (AlAT, AspAT, INR, bilirubin, complete blood count, albumins) and copper metabolism (ceruloplasmin, 24h-urine copper, liver copper) data before pharmacological therapy was started was compared between both groups. U-Mann-Whitney test was used and P< 0,05 was regarded as significant.

Results: No changes were found between demographic, clinical and laboratory data between both groups. Severe group had significantly lower concentration of ceruloplasmin: 9; 3; 11 [median; Q1; Q3] vs. 15; 11; 18. No differences in 24h-urinary and liver copper were found.

Conclusions: Nonsense and frameshift mutations disturb copper metabolism more than missense ones. They have no influence on clinical presentation of WD in Polish children.

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Objectives and Study: Autoimmune hepatitis (AIH) is a progressive inflammatory disease necessitating prompt immunosuppressive treatment. Cyclosporine (CSA) could be an alternative to prednisone (PDN) and azathioprine (AZA), but its unknown long-term safety and efficacy have limited its use. We examined the long-term outcome of patients with AIH treated with CSA for at least 4 years.

Method: Observational study, conducted retrospectively by chart review (1993-2004) and prospectively (2004-2015). Twenty patients (15 females) were included, 15 affected by classical AIH and 5 by autoimmune hepatitis/autoimmune sclerosing cholangitis overlap syndrome (OVLS). Median age at diagnosis: 9.5 years (1.4-14.2). CSA was administered orally for a median period of 6.3 years (4-15.5), either as first- (n=12) or second-line (n=8) therapy, alone or in combination with AZA or mycophenolate mofetil (MFM) and/or PDN. CSA target trough levels were the following: initial 150-200 ng/mL, after remission 100-150 ng/mL, after 1 year of treatment 50-70 ng/mL. Ursodeoxycholic acid was added in OVLS patients. Response to treatment was defined as complete remission (normalization of clinical and laboratory features), incomplete response (partial clinical and laboratory improvement with or without the need for second or third-line therapy) or treatment failure. To evaluate CSA adverse events serum creatinine levels, glomerular filtration rate (GFR), blood pressure, gingival hyperplasia, hypertrichosis and neurological signs were routinely assessed.

Results: CSA determined initial clinical and biochemical remission in all patients independently of the degree of hepatic impairment. No statistically significant difference was found in the time to achieve remission in AIH and OVLS patients and in patients receiving CSA as first- and second-line treatment. Overall, at the end of a median follow-up of 8.6 years (4-20.4), all patients are alive with their native liver; 15 are in complete remission, 2 present incomplete response to treatment. Three patients (2 with OVLS) are listed for liver transplantation 6.3, 11.2 and 14.4 years after diagnosis. CSA determined long-term sustained clinical and biochemical remission in more than 80% of the treatment naive patients, alone or in combination with AZA or PDN. Shift to AZA monotherapy was achieved in 60% of these patients and even after CSA withdrawal no relapse occurred. One patient (8%) has successfully been out of therapy for the past 6 months. In patients who received CSA as second-line treatment, CSA allowed complete prolonged remission in 62.5% of cases, alone or in combination with AZA and/or PDN and/or MFM. CSA side effects were mild and transitory in all patients, spontaneously, after dose tapering or, in 1 case, after CSA withdrawal. Transient hypertrichosis and moderate gingival hyperplasia were the most frequent side effects occurring in 45 and 55% of patients, respectively. A transient mild GFR reduction occurred in 2 patients (10%). Median GFR was not statistically different at the beginning and end of treatment for all patients. None presented with hypertension.
Conclusion: CSA is a highly effective and safe long-term treatment for AIH in pediatric patients. Monitoring potential adverse effects, and tailoring the treatment remain key points during CSA administration.

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A mother-infant pair with a concomitant diagnosis of cirrhotic wilson disease: An exceptional case of a recessive disorder in consecutive generations

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Objectives and Study: Nowadays the value of genetic testing has moved way beyond the confirmation of a clinical suspicion. Diagnosis by whole-exome sequencing (WES) allows to broaden the phenotype of known genetic conditions. We report the case of an infant referred to our centre because of neonatal cholestasis that progressed to cryptogenic cirrhosis and end-stage liver disease in whom WES revealed an unusual familial presentation of Wilson disease (WD).

Method: Family history, demographic, clinical and laboratory data of the patient were recorded. The trio-WES analysis was performed using the Agilent SureSelect Clinical Research Exome v2.0 enrichment kit, following our "urgent" protocol. Data were analysed and filtered according to our standard protocol. The variants were prioritized on the basis of the patient clinical presentation.

Results: A female infant from non-consanguineous parents presented with jaundice in ABO-incompatibility, and developed cholestasis. She had normal GGT, high serum bile acids, AST > ALT. Liver biopsy showed diffuse giant cell transformation, canalicular cholestasis, moderate lobular activity, minimal steatosis, extramedullary haematopoiesis. She was started on ursodeoxycholic acid. At 7 months of age, she had cirrhosis, with total/conjugated bilirubin 22/20 mg/dL, PT INR 1.9, AST/ALT x 4/1.5 ULN, normal GGT, renal failure and tense ascites. She appeared severely hypotonic, and had also laryngotracheomalacia, Coombs' haemolytic anaemia, central hypothyroidism. After surgical closure of a patent ductus arteriosus, she was listed for liver transplantation (LT) with a PELD of 34. The work-up showed normal virology, serum alpha-1-AT, amino acids, pyruvate, lactate, acyl-carnitine profile, transferrin isoelectrofocusing, erythrocyte GAL-1-PUT, chloride sweat test, urinary organic acids, beta-glucosydase, acid sphingomyelinase and lysosomal acid lipase activity. The urgent trio-WES analysis of the girl and both parents revealed in five working-days that the girl was compound heterozygous for two mutations in the gene ATP7B causing WD (p.His1069Gln + p.Gln7fs); the mother was homozygous for p.His1069Gln, and then was confirmed having WD. We assumed that the picture was the result of a in utero copper overload of a WD foetus in a WD untreated mother: ceruloplasmin was 39 mg/dL (ULN > 20); 24h urine copper 100 µg/24h (299 µg/24h after penicillamine challenge); free serum copper 18 µg/dL (n.v 5-15). She was started on penicillamine and transplanted soon after. Liver copper was 350 µg/g dry weight. She is alive and well 6 months after LT with complete neurologic recovery. The mother is well under penicillamine.

Conclusion: The occurrence of WD genotype in consecutive generations is exceptional and associated to an atypical presentation that would not have been diagnosed before the advent of an unbiased trio-WES analysis. This is the first report of a WD foetus from an untreated WD mother in which an intrauterine copper exposure in addition to the disrupted copper handling have led to early severe liver injury presenting as neonatal cholestasis.

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Objectives and Study: To determine the etiology of Acute Liver failure (ALF) and the possible prognosis factors in children.

Method: Retrospective cohort study. One hundred pediatric patients with ALF were included from January 2001 to January 2016. Medical records were reviewed for demographic, laboratory and clinical data.

Results: 100 children (51 female), median age 60.6 months, range 1-192 month. 66 (66%) patients recovered spontaneously, 34 (34%) patients died without transplantation. Specific causes of ALF could be identified as infectious diseases 49% the most frequent Hepatitis A virus infection, immunologic diseases 10%, metabolic diseases 7%, toxic liver injury (paracetamol) 2% and indeterminate 33%. Conjugated hyperbilirubinemia, low albumin, high ammonia, and prolonged INR were associated with worse outcome (p value &LT; 0.05. Wilcoxon rank sum Test). Hepatic encephalopathy results in a bad prognosis factor. Comparison of mortality according to the presentation time refers that subacute and hyperacute presentations have statistical significance of relative risk (p &LT; 0.05) (hyperacute: 1-7 days, acute 8-28 days, subacute 22-182 days).

Conclusion: In developing countries Hepatitis A virus is the most common known cause of ALF. Hyperbilirubinemia, high ammonium, low albumin levels, severe coagulopathy, a subacute and hyperacute presentation, and severe encephalopathy, may be prognostic value to predict outcome.

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Diagnostic tools in autoimmune hepatitis: discrepancies in scoring systems

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Objectives and Study: The scoring system for the diagnosis of autoimmune hepatitis (AIH) established by the international Autoimmune Hepatitis Group (IAIHGSS) in 1990s had been developed based on adults’ data and used for them. In 2007 a Simplified scoring system (SSS) was proposed. Both scores are still not adapted for paediatric use and their results are sometimes different. Our objective was to compare IAIHG Scoring System and SSS regarding the accuracy of diagnosing AIH in children.

Method: We conducted a retrospective longitudinal study from the 1st of January 2010 to the 1st of October 2017 in the Paediatric Department of “Grigore Alexandrescu” Emergency Children’s Hospital in Bucharest. We included 28 children diagnosed with AIH, out of which 12 were identified with other autoimmune associated disorders. We compared results of IAIHG 1999 revised Scoring System and SSS applied in all 28 children. A score of more than 15 points by IAIHG Score and more than 7 points by SSS supports a definite diagnosis; a score of 10 to 15 points and 6 points supports a probable diagnosis using IAIHGSS respectively SSS.

Results: Of the 28 children with AIH, 35.7% (10) were classified as having definite AIH, 50% (14) were classified as having probable AIH while 14.3% (4) had nondiagnostic scores using the IAIHGSS. The SSS established AIH diagnosis in only 57% (16) of children, with half classified as definite AIH and the other half as probable AIH. Of the 10 children classified as having definite AIH using IAIHGSS, 6 had a definite diagnosis and 4 had a probable diagnosis according to SSS. Among the 14 children diagnosed with probable AIH by IAIHGSS, 2 children were graded as definite AIH and 3 as probable AIH by SSS, while the great amount of 9 children were classified as not having AIH. Of the 10 children classified as having definite AIH using IAIHG score, 4 were downgraded to probable AIH using SSS. In the group of 14 children with probable AIH classified by IAIHGSS, 2 were upgraded to definite AIH, 9 were downgraded to not having AIH while 3 remained in the same category when using SSS. Of the 4 children who had nondiagnostic scores using IAIHGSS, 1 was upgraded to probable AIH using SSS while 3 had no change. The upgraded case by SSS was a boy with elevated alkaline phosphatase (ALP); these 2 parameters - male sex and ALP made him lose points in IAIHGSS, while SSS does not include these variables. All the children with nondiagnostic scores using IAIHGSS had autoimmune associated disorders (AAD) as follows: 1 ulcerative colitis, 1 hemolytic autoimmune anemia and 2 overlap syndromes with sclerosing cholangitis. According to SSS, 9 out of 12 children with AAD did not have AIH, leading to a sensitivity of 25% of SSS when used in AIH plus AAD cases. Overall sensitivity of IAIHG score was 85% while the sensitivity of SSS was approximately 2/3 of the IAIHG scoring system (57%).

Conclusion: The 2 scoring systems for the diagnose of AIH showed major discrepancies in classifying patients as having definite, probable AIH or not having AIH. The Simplified Scoring System has a low sensitivity, not diagnosing almost half of the cases. In cases with AIH and AAD both scores have a low sensitivity, with SSS missing most of the cases. There is room for improvement in scoring systems for AIH diagnose.

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Chronic hepatobiliary disease in childhood

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Chronic hepatobiliary disease (CHB) is defined as progressive liver disease which lasts over a period of 6 months. In which, hepatobiliary lesions identified by biochemical, hematological, histopathological, genetic, and imaging tests. CHD is not a common issue in children and its etiology differs from adults. Some childhood CHD caused by specific diseases process that only manifests in childhood as biliary atresia, metabolism diseases as Wilson...But most of CHD will result in cirrhosis and the end stage liver disease if it is not properly diagnosed and treated.

**Objectives and Study:** To understand the causes of chronic hepatobiliary disease in children. Analyse data of the patients who were diagnosed chronic hepatobiliary disease at the Vietnam National Children's Hospital during the period 2010 to 2017

**Method:** Prospective descriptive case series study

**Results:** 995 children who were eligible the criteria of chronic hepatobiliary disease involved this study. The most common caused of CHD in infancy were biliary atresia 291 (31.5%), paucity bile duct 16 (1.7%). Diseases related to genetic metabolic disorders: NICCD 186 (20.3%), Wilson 92 (9.9%), GSD 47 (5.1%), Alagille 27 (2.9%), PFIC 12 (1.3%), ARC 11 (1.2%), other IME 31 (3.4%). Chronic hepatitis B is only 6.6% with 61 patients, chronic hepatitis C 17 (1.8%). Autoimmune Hepatitis 3.5%, NASH 2.3%. Other rare diseases, such as Caroli 1.3%, congenital cirrhosis 0.6%, primary sclerosing cholangitis was only 1 patient, cryptogenic portal hypertension 6, 5%.

**Conclusion:** Thanks to the advances in biochemical analysis and molecular genetics, etiology of Vietnam children's chronic hepatobiliary disease was changed in recent years. The results showed that CHB caused by chronic viral hepatitis were not the most common causes as adults. The childhood chronic hepatobiliary disease which related to genetic disorders and congenital abnormalities is the largest group. Most children with chronic hepatobiliary disease will progress to cirrhosis or end stage liver disease in adults. Therefore, this group not only needs treatment in childhood but also needs to be monitored in adulthood.

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Bone mineral density evaluation in children with autoimmune liver disease: a single centre experience

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Objectives and Study: Autoimmune liver disease (AILD) is a chronic and progressive inflammatory liver disease. Immunosuppressive treatment strategy usually includes steroids and azathioprine. It is well-known that long-term steroid treatment can cause decrease in bone mineral density. For this reason, we aimed to evaluate bone densitometry at AILD diagnosis and during the follow-up in our paediatric series.

Method: A retrospective evaluation of 25 AILD children referred to our Paediatric Liver Centre (12 males and 13 females; mean age at AILD diagnosis: 9 years and 1 month, age range: 4 years and 7 months - 14 years and 3 months) was carried out. Bone densitometry was performed in all patients at AILD diagnosis and during the follow-up. All the children were treated with steroid therapy, except one who took cyclosporine. Calcium and vitamin D supplementation was prescribed according to serum levels in all patients during steroid therapy.

Results: At AILD diagnosis the bone densitometry showed abnormal Z-score values (osteopenia or osteoporosis) in 13/25 patients (52%); two of them presented severe osteoporosis and alternative therapy to steroids was chosen (i.e. cyclosporine). Among these 13 children, 4 of them (31%) presented an associated inflammatory bowel disease (IBD). In the remaining 12 children with normal initial bone densitometry values, no worsening was noticed during the follow-up. Only one patient necessitated bisphosphonate therapy, with progressive increase in bone mineral density and no collateral effects. No vertebral fracture was observed during the follow-up.

Conclusion: Our study showed a high percentage of bone demineralization at AILD diagnosis, particularly in children with IBD. These data could help the clinicians in the choice of the appropriate immunosuppressive therapy, avoiding steroids in the most severe cases. Bisphosphonates are a possible therapeutic choice when indicated. It is important to perform bone densitometry before starting steroid therapy and during the follow-up.

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"Outpatient follow up of autoimmune liver disease: how family friendly is our service?"

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Objectives and Study: Current National standards/guidelines for Specialist Liver Disease highlight importance of a family friendly service. It is achievable if Specialist Centres and local teams work closely together through agreed clinical networks and deliver services as close to home as possible. The recent Royal College of Paediatrics and Child Health(UK) and British Society of PGHAN standards suggest (i)services are delivered within clinical networks, (ii) access is equitable and designed across geographical, political and NHS/health board boundaries through network, (iii) gastroenterology network is linked to a lead specialist centre for Hepatology and includes agreed patient pathways, specialist outreach clinics and shared care arrangements.

Aims: To determine whether outpatient pathway for children with autoimmune liver disease (AILD) is delivered in accordance with standards.

Objective: To assess care pathways for all children with AILD referred to a single UK Hepatology Specialist centre.

Methods: All children seen by a Specialist Liver Service for 5 years between 2011 and 2015 were identified. Retrospective data collection performed using electronic patient records to determine follow up arrangements until Dec 2015 or discharge. Children local to centre, those with IBD or SLE or those assessed for transplant were excluded.

Results: 71 children were identified, of whom 20 were from own region and 51 were extra-regional referrals (from 6 regions) where regular outreach clinics were in place. Of 20 referred within own region, 18 had follow up (FU) exclusively at specialist centre, and two had shared FU with referring hospital. 28/51 extra-regional referrals were from tertiary gastroenterology centre, and 23/51 from secondary care. 26/28 (93%) referred from tertiary centre had follow up only at outreach clinic +/- secondary care, two had FU at both outreach clinic and specialist centre (for transition education & for complex disease). All 23 referred from secondary care were from 3/6 regions, and represented 40%, 67% and 81% of their referrals. 12/23 (52%) had ongoing specialist centre FU: 8 with shared care at tertiary centre and/or secondary care hospital. 11/23 (48%) had FU only at tertiary centre or outreach clinic and/or secondary care hospital. There were no formal shared care documents except for an outreach outpatient clinic standard from the Specialist Centre. Through clinical networks, all extra-regional patients had care shared with local or tertiary services, but 14/51 (27%) still had appointments at specialist centre. Ongoing specialist centre FU was more common following extra-regional secondary care rather than tertiary centre referral (52% v 7%). For referrals from within local region, only 2/18 had shared care with secondary centre. Pathways were varied, being tailored according to tertiary and secondary service expertise, geography and patient preference.

Conclusion: Current standards are partially met when applied retrospectively to specialist service provision. Effective utilisation of outreach clinic and enhanced involvement of tertiary centres may reduce the need for long distance travel for families. The need for shared care documentation and improved network arrangements in some areas is highlighted to make services more family friendly.

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Feasibility and intra-observer reproducibility of VTQ in children

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Pediatric chronic liver diseases are a public health issue. The use of ultrasound based elastographic techniques as non-invasive methods of liver fibrosis assessment in children has gained a lot of attention. Still, there is limited data regarding feasibility and reproducibility of elastography in the pediatric population.

Objectives and Study: We aimed to investigate the feasibility and intra-observer reproducibility of VTQ in children.

Method: We conducted a prospective study which included 113 children (age range: 6 months-20 years, mean age 10.87±4.23 years, 47.8% girls, mean body mass index (BMI) 23.65±7.8 kg/m2). We divided our study population into children with diffuse liver disease (DLD, n= 53) and controls (n=60). We used a point shear wave elastography technique: Virtual Touch Tissue Quantification- VTQ (Acuson S2000, Siemens), with a 4C1 probe. We performed 10 measurements for each child and calculated the respective medians and IQRs. We defined as unreliable a result with an IQR/median ratio above 30%. Furthermore, we considered a measurement failed, if "X-X-X" was displayed on the screen. We defined as unquantifiable an evaluation with more than 4 failed measurements. For the intra-observer reproducibility analysis we compared the first five and last five measurements using Interclass Correlation Coefficients (ICCs) and the Bland-Altman plots.

Results: We obtained in unquantifiable results in 2.65% children (3/113). 8.85% (10/113) of the results were unreliable. The overall median and the medians of the first five and last five measurements were similar in the study population (1.2 (0.33) m/s vs 1.2 (0.37) m/s vs 1.2 (0.41) m/s, p= 0.65) and across study groups: children with DLD (1.22 (0.45) m/s vs 1.23 (0.41) m/s vs 1.24 (0.47) m/s, p= 0.73) and controls (1.16 (0.35) m/s vs 1.16 (0.34) m/s vs 1.18 (0.38) m/s, p= 0.74). The agreement between the first five and the last five measurements was excellent overall (ICC= 0.895 (0.847-0.928)) and across study groups: DLD (ICC= 0.948 (0.911-0.970)) and controls (ICC= 0.786 (0.631-0.872)). The mean difference between the first five and last five measurements was 0.03±0.31. The 95% upper and lower limits of agreement (LOA) were 0.59 and -0.65, respectively. The 95% upper and lower LOA in the study groups were: children with DLD 0.42 and -0.37; controls 0.69 and -0.85.

Conclusion: VTQ has great feasibility in children and may be used in the pediatric population with high intra-observer reproducibility.

Disclosure of interest: Sporea Ioan has received financial support (congress travel grant or speaker fee) from Philips, Siemens, General Electric, Abbvie, Zentiva, Bristol Meyers Squibb

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Liver injury in hemophagocytic lymphohistiocytosis

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Objectives and Study: Hemophagocytic lymphohistiocytosis (HLH), primary or secondary, is a life-threatening hyperinflammatory syndrome that occurs in many underlying conditions in associations with a variety of triggers. Hepatic dysfunction was reported in almost all cases of HLH, varying from mild liver injury to hepatic failure. The aim of the study is to identify the type of HLH (primary or secondary), to analyze the clinical and laboratory liver parameters, and to correlate them with the evolution.

Method: 16 patients between 2 months and 8 years of age were diagnosed with HLH in the period 1995-2017. They fulfilled at least 5 from 8 HLH 2004 protocol criteria (fever, splenomegaly, cytopenia on at least 2 lineage, ferritin>500ng/ml, hypertriglyceridemia and / or hypofibrinogenemia, hemophagocytosis, low or absent NK-cell activity, sCD25 >2400). In all patients we analyzed the liver parameters, clinically and biologically: SGPT, SGOT, direct bilirubin, yGT, LDH, triglyceride, D-dimer and abdominal ultrasound.

Results: 10 patients (62,5%) had primary HLH (1 Griscelli, 2 Chediak-Higashi syndrome, 1 case FHLH2, 3 cases with probability of FHLH, 2 SCID, 1 Nijmegen syndrome) and 6 patients (37,5%) had secondary HLH (2 leishmaniosis, 1 Kawasaki, 1 systemic JIA, 2 leukemia). All of them had fever and hepatomegaly. 87,5% had increased transaminases, 62,5% increased direct bilirubin, 75% increased yGT, 100% increased LDH and D-dimer and 87,5% had increased triglyceride. The global mortality rate was 56,25%, higher (70%) in primary HLH than in secondary HLH (33,34%). Unfavorable prognostic factors were: SGPT (with a medium value 9,33 times the upper limit of normal values in deceased patients / 5,81 times the upper limit of normal values in alive patients), SGOT (34,2/16), direct bilirubin (13,87/3,88), LDH (6,3/2,9) and D-dimer (12,9/7,5). Ultrasound revealed in all patients hepatosplenomegaly, coarse hepatic echotexture with multiple &LT; 1 cm hypoechoic focus in the liver, thickening of the gallbladder wall, increased periportal echogenicity and enlarged periportal lymphnodes.

Conclusion: Liver injury with coagulopathy is a common feature in HLH and was present in all our patients. Even if, the liver parameters are not criteria diagnosis of HLH, they are very suggestive for the diagnosis in each case of systemic inflammation with hepatomegaly, jaundice and cytopenia, and are crucial for the treatment decision, especially in the cases which do not fulfill HLH 2004 criteria.

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Chronic liver involvement in urea cycle disorders on medium-long term follow-up

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Objectives and Study: The long-term treatment of urea cycle defects (UCD) is based on a low protein diet combined with essential amino acids supplementation, arginine and/or citrulline therapy and ammonia scavengers drugs, benzoate and phenylbutyrate; in some cases liver transplantation (LT) is indicated. The increased survival of UCD patients has led to the appearance of new clinical manifestations on long-term disease course. Despite historical evidence of hepatic involvement, information and its characterization are often anecdotal, especially in the long term.

Methods: A cross-sectional study on the long-term hepatic outcome was conducted in 52 UCD patients (median age at last evaluation of 21 years, range 3-49), followed at our center for a median time of 13 years. Patients cohort included: 18 OTC [8 males/10 females, 2 diagnosed by neonatal screening (NBS)], 14 ASL (2 by NBS), 10 ASS (4 by NBS); 8 HHH syndrome, 1 CPS; 1 argininemia. Seven patients were LT [4 ASL, 2 OTC (1M/1F), 1 CPS]. Data were collected at last outpatient evaluation and included full metabolic profile (ammonia, aminoacids, orotic acid), parameters of liver function, abdominal ultrasound, information on dietary and pharmacological treatment, anthropometric measures, and bioimpedance analysis (BIA).

Results: Mean plasma ammonia was 32.8 µmol/L (range 7-96, normal < 40); glutamine 945 µmol/L (range 594-1295, normal < 800). Glutamine levels were significantly higher in patients with HHH syndrome than other groups (p: 0.01), while ammonia did not differ among analyzed groups. No correlations were found between protein intake and ammonia (p: 0.49; R: 0.01) and glutamine (p: 0.25; R: 0.03) values. Transaminases (AST, p: 0.01, ALT, p: 0.02) and GGT (p: < 0.01) were significantly increased in patients with ASL. In addition, ASL patients showed significantly higher levels of triglycerides (p &LT; 0.01) and uric acid (p &LT; 0.01) compared to all other UCDs. In this disease, mean insulin was 18±6 pmol/L, HOMA-index 4.5±1.2, and all patients showed at BIA significantly lower levels of total body water (p &LT; 0.01) and phase angle (p &LT; 0.01) than OTC patients, with no differences in BMI. Abdominal ultrasonography showed a fatty liver with evidence of severe fibrosis/cirrhosis in 10/14. After LT, uric acid and triglycerides were significantly lower than pre-LT (p&LT; 0.01). Patients with HHH syndrome showed higher levels of serum bile acids compared to other UCDs (23.2±9.0 vs. 4.0±1.4 µmol/L, p.&LT; 0.01). Furthermore, values of α-fetoprotein were significantly elevated in HHH than in ASL (37.5 ±12.0 vs. 2.9±1.0 ng/ml, p.&LT; 0.01), in the absence of focal liver lesions; 80% of HHH patients showed at liver ultrasounds mild hepatomegaly with hyperechoic signal. All patients with OTC and ASS deficiency showed normal liver enzymes, with mild hepatomegaly in 30% and 40% of patients, respectively.

Conclusion: Different form other UCDs, ASL and HHH syndrome may be associated with long-term chronic liver disease; ASL patients also present some clinical and biochemical features of metabolic syndrome which seems to have a beneficial impact by LT. We also demonstrate that HHH syndrome only, is associated with high levels of serum biliary acids (and α-fetoprotein), whose role in liver disease still need to be elucidated.

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Entecavir monotherapy results in complete remission of Hepatitis B virus-related membranous nephropathy in a paediatric patient

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Objectives and Study: Chronic hepatitis B virus infection (CHB) affects approximately 350 million people worldwide, including approximately 1.5 million in North America. CHB is a leading cause of morbidity and mortality in children worldwide. Children with CHB are at high risk of long-term complications including cirrhosis and hepatocellular carcinoma. Renal disease is an extrahepatic manifestation associated with CHB. Entecavir (ETV) is a nucleoside analogue use for the treatment of CHB with evidence of active viral replication, persistent elevation of alanine aminotransferase (ALT) and histologically active disease.

Method: We report a case of a child with Hepatitis B virus-related membranous nephropathy (HBV-MN) successfully treated with ETV monotherapy.

Results: An 8-year-old girl with vertical transmission of CHB developed edema, hypoalbuminemia, proteinuria and microscopic haematuria. A renal biopsy led to a diagnosis of HBV-MN. She was positive for hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg); hepatitis B viral DNA load (HBV DNA) level was >170,000,000 IU/mL. Liver biopsy showed portal inflammation (Grade 2 - 3) and bridging portal fibrosis (Stage 3). She was started on Entecavir (0.015 mg/kg/day) 0.4 mg once daily. After 2 months of treatment, proteinuria resolved, HBV-DNA was not detected in the blood, and the ALT returned to normal levels. After 5 years of entecavir therapy, virological tests revealed HBeAg seroconversion.

Conclusion: Entecavir monotherapy induces and maintains complete remission of Hepatitis B virus-related membranous nephropathy.
Wilson disease (WD) is a rare disease, which has a prevalence of approximately 1 in 30,000 live births. WD is an autosomal recessive inherited disorder caused by dysfunction of the copper transporter ATP7B. The disease has wide spectrum clinical manifestation, two main manifestations of WD is chronic liver disease and neuropsychological signs.

**Objectives and Study:** Study on group of 82 Wilson patients under 18 years old to determine clinical, biochemical manifestations and genetic feature

**Method:** Retrospective study

**Results:** The mean age of diagnosis was 11.6 ± 0.8 years. Some common clinical presentation of WD in pediatric patients: Chronic liver disease with prolong elevation of transaminase (84%), hepatomegaly (6.1%), splenomegaly and portal hypertetion symptoms (3.7%). Some patient had onset as hepatic failure (22%). There were only 7.3% patients had neuropsychiatric symptoms and 8.5% had neuropathic symptoms. The most common biochemical characteristic are decreased of ceruloplasmin serum level (98.8%), 24-h urinary copper excretion (100%). Only 9.8% patients had presence of Kayser-Fleischer rings. There were 52 patients of group have been tested for genetics. The analysis mutations of ATP7B gene showed 92.3% patients had been detected mutations of this gene. In which, 26 patients homozygotes (54.2%), 11 compound heterozygous (22.9%), 7 patients with heterozygous (14.6%) and there were 4 patients no detected any mutations of ATP7B gene (8.3%). During 7 years of treatment with chelating therapy and follow up, there were 87.8% of the patients had a stable or improved course of the disease. There are 10 patients (12.2%) has had cirrhosis liver and chronic liver disease, in which 5 patients (6.1%) were died by end stage of liver disease.

**Conclusions:** Pediatric patients with Wilson's disease having predominantly hepatic symptoms, most of them tolerated chelating therapy and have a satisfactory outcome. We should pay attention to diagnosis of Wilson in patients who has chronic liver disease or unknown origin hepatic failure.

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HEPATOLOGY - General Hepatology

H-P-074

Long term outcome of children with PFIC - A single centre experience

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Progressive familial intrahepatic cholestasis (PFIC) is an inherited disease typically presenting in infancy with varying degrees of liver disease. Treatment options are dependent on genotype. Historically three genotypes were common (PFIC1-ATP8B1, PFIC2-ABCB11, PFIC 3-ABCB4). Recently new genotypes (TJP2 and DCDC2) have been identified.

Objectives and Study:
(1) Identify genotype/phenotype correlation with clinical course and medical/surgical intervention necessary
(2) Identify sub-group of patients who carry a single genetic mutation (heterozygous carriers) and whether this is linked to outcome

Methods: Retrospective descriptive study. Inclusion criteria: All patients of BCH Liver Unit with a genetic or phenotypic diagnosis of PFIC presenting from 1984 - 2017. Exclusion criteria: Patients who have received an alternative diagnosis. Data collected: gender, family history of liver disease, consanguinity. Medical and surgical management of condition including clinical trial involvement, cholecystectomy, external biliary drain insertion (EBD) and liver transplantation (LT). Genetic mutation analysis was also assessed where available.

Results: 80 children were identified as having a diagnosis consistent with PFIC or BRIC, Table 1. 54% were female and 28 children were born of a consanguineous marriage (33%). Following genetic screening, a confirmatory genetic mutation analysis was available in 30/55 patients. For the purpose of this review we have focussed on patients with confirmatory homozygous/heterozygous mutations. Patients with phenotypic features but no genetic diagnosis excluded from further analysis.

<table>
<thead>
<tr>
<th></th>
<th>PFIC1</th>
<th>PFIC2</th>
<th>PFIC3</th>
<th>unknown</th>
<th>BRIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>8</td>
<td>20</td>
<td>2</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>Median age at diagnosis (days)</td>
<td>213 (range 12-416)</td>
<td>66 (range 9-1003)</td>
<td>29 (range 29-47)</td>
<td>49 (range 13-250)</td>
<td>5110 (range 40-10427)</td>
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<tr>
<td>Genetic confirmation</td>
<td>7</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clinical presentation (no genetic mutation identified)</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Intractable pruritis (genetically confirmed patients)</td>
<td>7</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>EBD in pt with genetic mutation - median age (years) at</td>
<td>3 (3.2) Range 1.9-4.1</td>
<td>6 (4.5) Range 2.7-6.4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
In our cohort, PFIC1 presented earlier - which is not consistent with literature. Age at presentation had an effect on mortality. Earlier presentation found to be significantly associated mortality (p< 0.01).

There were no significant associations between age of presentation and need for transplant or medical intervention. Patients with PFIC1 were more likely to require EBD or LT, 37.5% and 75% respectively. Leading indication for transplant (13/14 children) with genetically confirmed PFIC was progressive liver disease with intractable pruritus. Two patients presented with acute liver failure (ALF) on a background of chronic liver disease, genetics confirmed one patient had PFIC 1, the other PFIC 2. One patient was listed for transplant following intractable variceal haemorrhage.

8 patients were heterozygous for at least one mis-sense mutation of uncertain clinical significance, but not at significantly higher risk of poor outcome compared to those without identified genetic mutation.

13 patients presented with Benign Recurrent Intrahepatic Cholestasis (BRIC). They typically presented in adolescence, with identified triggers including medications e.g. OCP in 9 patients.

**Conclusion:** The outcome of children with PFIC is dependent on age at presentation and genetic diagnosis. Clinicians should be aware that they can present with acute on chronic liver failure. There are a number of medical and surgical interventions which may alleviate symptoms, however ultimately most of the children may require LT, especially with genetically confirmed PFIC1. Presence of heterozygous mutations does not appear to affect overall outcome or predict phenotype.

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Hyponatremia due to hypervolemia and survival with native liver in paediatric patients with cirrhosis secondary to biliary atresia

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Objectives and Study: To evaluate the prevalence of hypervolemic hyponatremia in children and adolescents with a diagnosis of cirrhosis secondary to biliary atresia, followed at the pediatric gastroenterology unit of a tertiary hospital and to estimate the loss of the native liver up to three months after the first episode of this event.

Method: Single-center study, based on analysis of historical data. From January 2000 and December 2016, we reviewed the electronic records of all patients up to the age of 18, both genders, diagnosed with cirrhosis (clinical-laboratory, ultrasonographic and / or histological criteria), no underwent to transplantation. The diagnosis of biliary atresia was confirmed by trans-operative cholangiography and histology. The native liver loss was defined as patient death or liver transplantation and compared with patients with serum sodium concentration >130 mEq/L.

Results: Hundred thirty-three patients with AB cirrhosis were identified, of whom 53 developed hypervolemic hyponatremia (prevalence of 39.8%). Of these, 46 lost their native liver (86.8%); 19 (35.8%) underwent liver transplantation, and 27 (50.9%) died. Prevalence rates of the native liver loss in non-hyponatremic patients were 56.2% (45/80): 37 (82.2%) progressed to transplantation and 8 (10%) died. Kaplan-Meier survival analysis demonstrated that patients with hyponatremia had decreased pretransplant survival compared with patients with serum sodium >130 mEq/L (p &LT; 0.000). At 180 days, native liver survival was highest in patients with sodium values between 125-129 mEq / L (p &LT; 0.000). There were no significant differences between these groups regarding serum levels of total bilirubin, creatinine, INR, the presence of ascites, refractory ascites, hepatic encephalopathy and Child-Pugh classification.

Conclusion: The prevalence of hypervolemic hyponatremia in the studied group was similar to that reported in the population of cirrhotic adults, with an impact on the native liver loss.

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**HEPATOLOGY - General Hepatology**

**H-P-076**

**Is NTCP deficiency a cause of failure to thrive?**

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**Objectives and Study:** Very little is known about deficiencies of bile acid transporters on the basolateral side of hepatocytes. In 2015 Vaz et al. published a first case of SLC10A1 deficiency causing hypercholanemia with normal bilirubin and autotaxin levels. Clinically their index patient presented with failure to thrive, but without pruritus or jaundice (Vaz et al. 2015). Deng and Liu et al. added to the initial description with another case and a small series (Deng et al. 2016, Liu et al. 2017). However, the full spectrum of clinical presentation of mutations in *SLC10A1* is not known. Liver histology of patients with sodium-taurocholate cotransporting polypeptide (NTCP) deficiency has not yet been reported and the genotype-phenotype correlation is not known. We present a patient with a NTCP deficiency caused by a novel loss of function mutation in SLC10A1.

**Method:** Retrospective chart review of a female born in 2002 presenting with feeding disorder and failure to thrive leading to the discovery of liver disease of unknown etiology characterized by persistently elevated serum bile acids. A first liver biopsy is performed at a very young age. Ursodeoxycholic acid treatment is introduced and the liver panel is monitored on a regular basis. Clinically she is well. Her only complaint is an occasional constipation. At age 14, a second biopsy is performed. Finally, genetic analysis is performed.

**Results:** The liver panel including ASAT, ALAT, gamma-GT, total bilirubin and direct bilirubin is normal. Bile acids are chronically elevated, up to 70 fold. Autotaxin level is normal. The liver biopsy at 2 years of age shows unspecific degenerative hepatopathy with focal steatosis. The second liver biopsy at 14 years of age, is unremarkable. Genetic analysis reveals a homozygote 5bp deletion in the *SLC10A1* gene leading to a frameshift with alteration of the first stop codon predicted to lead to a complete loss of function.

**Conclusion:** We describe a new case of hypercholanemia due to a novel mutation of the *SLC10A1* gene coding for NTCP. The identification of this mutation leading to a complete loss of function confirms the major role of NTCP in hepatic bile acid uptake. Though the full spectrum of clinical presentation of NTCP deficiency is not known, we could hypothesize that there is a link with failure to thrive. We suggest taking NTCP deficiency into consideration when confronted with a patient presenting failure to thrive, unexplained anicteric cholestasis or when confronted with a liver biopsy showing mild steatosis of unclear etiology.

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HEPATOLOGY - General Hepatology

H-P-077

**Hepatitis C virus resistance associated substitutions in a 16-year-old adolescent failing ombitasvir/paritaprevir/ritonavir plus ribavirin**

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**Objectives and Study:** We describe the first case ever reported of a paediatric patient with chronic hepatitis C (CHC) who received the DAA combination of ombitasvir/paritaprevir/ritonavir plus ribavirin and presented treatment failure because of the emergence of viral resistance.

**Method:** In October 2015 a 16-year-old girl with hepatitis C virus (HCV) genotype 4 infection and compensated cirrhosis has been treated with the combination of ombitasvir/paritaprevir/ritonavir and ribavirin. HCV viraemia was 2,922,980 IU/mL before starting treatment and reached 105 IU/mL after 2 weeks of therapy. At treatment week 3, viraemia levels started increasing (1,900 IU/mL) and treatment was withdrawn after one more week (285,800 IU/mL). Resistance associated substitutions (RAS) analysis has been performed by Direct Sanger sequencing on plasma samples collected at baseline and treatment failure. Results have been interpreted by Geno2pheno web interpretation system.

**Results:** At baseline, the mutation scoring system detected the M28V RAS plus the Y93C substitution known to confer resistance to NS5A inhibitors in genotype 1 and the non-canonical substitution L30A. In addition, the D168H RAS was detected at failure but not at baseline. This mutation is presently considered to confer resistance to the NS3 inhibitor paritaprevir in genotype 4a.

**Conclusion:** This is the first reported case of resistance to DAA in an adolescent with HCV genotype 4 infection and compensated cirrhosis. The RAS analysis showed the presence of multiple substitutions responsible for ombitasvir/paritaprevir/ritonavir failure. Pre-existence and appearance of RAS is one of the most important factors limiting the efficacy of DAA. In children there is currently no recommendation to test for RAS before treatment with DAA. RAS analysis is clearly important to guide re-treatment after failure. Given that most children with CHC acquired the infection by mother-to-child transmission, if the mother has been already treated with DAA failing to eradicate the virus, testing RAS before starting treatment could be advised as the child could have acquired an HCV variant with the same resistance profile of the mother.

**Disclosure of interest:** Daniele Serranti and Giuseppe Indolfi are investigators in a study sponsored by Gilead Sciences (NCT02175758). The sponsor has no involvement in the realization of the present study.

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Correlation of APRI Index with Metavir Index in children with Neonatal Cholestasis without biliary atresia

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Objectives and Study: Neonatal cholestasis constitute for 19 to 33% of all chronic liver disease in India. Cholestasis leads to fibrosis of liver and ultimately cirrhosis. There are various methods of diagnosis of fibrosis of liver like fibroscan, APRI index, FIB-4, fibro index, forns index, heap score, magnetic elastography. Here we are comparing APRI index with METAVIR index in patients with neonatal cholestasis without biliary atresia and determining whether APRI index can be used as a tool to determine fibrosis in these patients.

Method: Patients with neonatal cholestasis without biliary atresia were included in the study. This retrospective analysis was done between 2009 and 2015. All patients underwent a liver biopsy and METAVIR index was calculated. APRI at the time of liver biopsy was determined.

Results: Forty eight patients were included in this study with mean age of 3.5± 2.8 months with a male: female ratio of 35:13. Metavir Index F0 was seen in was 32 (66.67%) patients, F1 in 6(12.5%), F2 in 4(8.33%), F3 in 0 and F4 in 6(12.5%) patients respectively. Mean APRI for F0-F3 was 1.38 and for F4 was 3.74 respectively. With an APRI of 1.38, the sensitivity and specificity to detect fibrosis/cirrhosis was 100% and 21.43% respectively.

Conclusion: APRI is not an effective tool to measure fibrosis or cirrhosis in patients with non-BA neonatal cholestasis in Indian children.

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Portal Biliopathy in children with Portal Vein Thrombosis: Clinical, laboratory and imaging characteristics

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Objectives and Study: Portal biliopathy (PB) is a term used to describe biliary tree changes secondary to compression by venous collaterals formed following portal vein thrombosis (PVT) that may lead to cavernous transformation of the portal vein (CTPV). The occurrence and significance of PB in children is not widely appreciated. The aim of this study was to assess the prevalence and clinical significance of portal biliopathy in children with portal vein thrombosis.

Methods: A retrospective analysis of all pediatric patients (ages 0-18) that were diagnosed with PVT between 2001-2016 in two medical centers. Imagining studies were reevaluated and detailed clinical and laboratory measures were recorded.

Results: Twenty children with PVT and sufficient records and imaging were found. The mean age at diagnosis of PVT was 7±6 years (range 0.4 months to 17 years). Thirty percent had history of prematurity and umbilical catheter. Eleven patients (55%) children had PB of which 7 (63%) showed evidence of PB on the first imaging. Splenomegaly was the most frequent presenting sign and was significantly more common in the PB group (10/11) than in the children without PB (3/9, p=0.02). CTPV was present in 16 of the twenty (11/11 in the PB group and 5/9 in the no PB group, p=0.026). Four children underwent a surgical portosystemic shunt; all four had PB.

Conclusions: Our study shows higher incidence of PB in children than previously reported. The presence of PB may signify worse prognosis for these children. Early identification of PB may enable earlier intervention with increased success and lower complication rate of PVT.

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Case report - Neonatal case of N-acetylglutamate synthetase deficiency and its management

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Objectives and Study: N-Acetylglutamate Synthetase Deficiency (NAGS) is a rare, autosomal recessive urea cycle disorder. Its clinical presentation is not different from the other hereditary hyperammonaemias. Deficiency of N-acetylglutamate is the most severe of the urea cycle disorders. Patients with complete NAGS deficiency rapidly develop hyperammonemia in the newborn period and present as a true neonatal emergency with high risk of insult to central nervous system and developmental delay. NAGS deficiency can be well managed with carbamylglutamate. Here we report a case of 2 days old neonate with NAGS deficiency who was managed with carbamylglutamate and other supportive measures.

Method: This is a case of 2-day-old term infant born of second degree consanguineous marriage. Child’s birth weight was 2.350kg. Child presented with vomiting, jitteriness and irritability. Mother had bad obstetric history with previous 2 male babies who died due to hyperammonaemia. The third female child is normal, both parents were carriers of NAGS deficiency gene. Child was admitted in NICU, Child’s septic workup was negative and liver function test were normal. The serum ammonia level were 252mg/dl. Patient was suspected to have NAGS deficiency in view of hyperammonaemia and positive family history. Blood was sent to differentiate Carbamylphosphate synthetase 1 (CPS-1) deficiency from NAGS. Child’s ammonia level rose to 2882mg/dl on day 5 of life. Child was successfully brought out from crisis with protein restricted diet, L-arginine, sodium benzoate, carbamylglutamate and other supportive treatment. Carbamylglutamate was started at dose 200mg/kg/day, the dose was later on titrated as per serum ammonia levels. Child had an episode of convulsion on day 8 of life and was started on anticonvulsant medication. There were no further episodes of convulsion. Child was discharged after 1 month with approximately 250 gm weight gain over birth weight. Child was on regular follow up. Weight gain, activity and growth was steady until 4 months of age when he had sudden bout of hyperammonaemia, unfortunately child died due to ventricular tachycardia and cardiac arrest.

Result: Child was brought out of acute neonatal hyperammonaemia crises without any clinically significant neurological deficit.

Conclusion: Hyperammonaemia in neonatal period should be aggressively treated, targeting multiple enzymatic pathway in urea cycle. Carbamylglutamate acts as structural analogue of N-acetylglutamate, which acts as allosteric activator of CPS-1. Hyperammonaemia crisis can be fatal but if managed has good outcome. NAGS deficiency though, rare can be well managed with carbamylglutamate.

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**HEPATOLOGY - General Hepatology**

H-P-081

**Outcome of chronic hepatitis b infection in foreign-born children followed in two national tertiary centres**

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**Objectives and Study:** After the introduction of the universal vaccination in industrialized countries, most of the children with chronic hepatitis B infection (CHB) are foreign-born patients who immigrated from endemic countries. Since long-term outcomes and indications to treatment are debated, understanding the role of ethnic and environmental factors on HBeAb (Sce) and HBsAb (SCs) seroconversion could be helpful in the clinical management of CHB in childhood. Aim of our study was to retrospectively evaluate the course of CHB in children born in HBV-endemic countries who were followed in our centres after immigration.

**Method:** The demographic, clinical, biochemical and virologic data of all the children with CHB (HBsAg+ for ≥ 6 months, confirmed HBVDNA and/or HBeAg positivity in blood/serum at the time of immigration) referred to two national tertiary centres between 2002 and 2017 were collected. Patients with normal ALT (< 45 IU/L) were classified as immunotolerant.

**Results:** Sixty-nine children (25 F) were enrolled at a median age of 4.7 years (3 months-15.5 years) and followed for 4.4 (6 months-14 years) years. The transmission was horizontal in 12 (17.4%), and supposedly vertical in 57 (82.6%). Fifty-six (81.2%) were adoptees, and all children were foreign-born: 40 (56%) were from Asia, 21 (30.4%) from Africa, 8 (11.6%) from Eastern Europe. No patients had HCV or HIV coinfection.

At entry, 63 children (91%) were HBeAg+/HBeAb-, while the remaining 6 were HBeAg+ with low viral replication and had Sce soon after the first visit. Out of 63 HBeAg+ children, 19 were immunotolerant, of whom 4/19 (21%) had eventual Sce. Among the remaining 44 immunoactive patients, 9/44 (20%) had Sce after a median time of 5.9 years, 13/44 (29%) normalized ALT, while 22 (50%) continued to have ALT elevation (median ALT 72 IU/L, range 47-172) for 3.4 years (6 months-11 years).

At the end of follow-up, all children had remained asymptomatic, and none of them died nor had developed chronic liver disease or hepatocellular carcinoma; 31% had raised ALT. No spontaneous SCs was observed, but 19/69 (27.5%) had Sce after a median time of 32 months (1 month-12 years); the overall Sce rate was 5.81%/year.

Patients who had Sce had higher ALT (73 ± 23 vs. 55 ± 26 IU/L, \(P=0.032\)) and lower serum HBVDNA (120 ± 115·10⁶ vs 169 ± 394·10⁷ IU/mL, \(P=0.010\)) at entry. Sce rates differed according to ethnic origin (Figure): children from Asia and from Eastern Europe had less Sce rate than African children (respectively 15% and 12.5% vs 57.1%, \(P=0.001\)). At univariate analysis, Asian children had a chance reduced by 4.6 to achieve Sce (OR=0.217; 95%CI=0.070-0.696; \(P=0.008\)), with a Sce rate of 2.88%/year.

**Conclusion:** Ethnic factors and laboratory features may help in identifying children with lower rate of spontaneous SC and viral clearance by five year from the first observation. Further studies are needed to better define such heterogeneity towards a more tailored clinical management.
Log-rank analysis of the HBeAb seroconversion curves according to ethnic origin.

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Changing of the hepatitis A seroprevalence in medical students in Bangkok, Thailand from 1981 to 2016

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Objectives and Study: The prevalence of hepatitis A virus (HAV) infection is decreasing in the newly developing countries including Thailand. This leads to growing population of susceptible adolescents and adults who tend to be symptomatic when the outbreak occurs. Medical care personnel, military assigned, children and workers in day-care facilities are candidates for outbreak prevention by hepatitis A vaccination. This study aims to determine the seroprevalence of anti-HAV in medical students and compare with our previous studies1-3 to understand the current situation of HAV infection and to develop an appropriate strategy for HAV prevention for this high-risk group.

Method: Sera from the first-year medical students at Chulalongkorn University between March and June 2016 were tested for anti-HAV by enzyme-linked immunosorbent assay. The cut-off level of anti-HAV > 10 IU/L was considered to be immunity. The result was compared to the previous studies during 1981 to 20011,2,3. All available vaccination books from medical students were assessed for the time and numbers of HAV vaccine they obtained. Medical students and parents also received the questionnaires regarding HAV vaccine and factors involved to complete.

Results: There were 176 medical students recruited into the study with aged 19.07±0.59 years and 50% were female. Of 111 (63%) had anti-HAV immunity. Of 66 (38%) students had a history of HAV vaccine documented in the vaccination books. Of those, 40 (61%) received full HAV vaccine series, 3 (5%) received 1 injection of HAV vaccine, 23 (35%) did not receive HAV vaccine, but 2 (3%) had HAV immunity. Calculated long-term efficacy of HAV vaccine is 98% in 15.55±2.44 years. For medical students whose vaccination books were not available, 56 (51%) had HAV immunity. There was a statistical difference in the HAV immunity between medical students who had vaccination books and whose vaccination books were not available (P=0.028).

Comparing to our previous studies1,2,3 as shown in figure 1, the seroprevalence of HAV immunity dramatically rises. The questionnaire demonstrated that most of the parents graduated with Bachelor degree or higher (n= 192, 89.5%) and the average income per capita was 17,000.76±194.22 USD per person per year (Thailand average income per capita is 5,908 USD per person per year4)
Conclusion: Seroprevalence of HAV immunity in medical students in the year 2016 was unexpectedly high compared to the previous trend. Obtaining HAV immunization might explain this high seroprevalence, not the natural HAV infection. Vaccination books were important as the history of vaccine recording and document had the good correlation with the results of anti-HAV testing. High parents’ educational level and economic status were the factors of HAV vaccine accessibility. Screening of vaccination books before HAV immunization or anti-HAV testing might have the cost-effectiveness to prevent HAV infection in hospitals in Thailand and other countries with a similar pattern of HAV epidemiology.

References:
4. Wolfram|Alpha Knowledgebase, 2017

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HEPATOLOGY - General Hepatology

H-P-083

Regression of fibrosis in pediatric liver diseases

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Objectives and Study: The concept of irreversibility of cirrhosis has been challenged in the recent past with literature in this regard, albeit still scarce, now being accumulated across all etiologies and geographical regions. Though literature is available in pediatric population regarding regression of hepatic fibrosis/cirrhosis in all etiological groups, it still remains grossly inadequate. We thus aimed to study this concept in our cohort of pediatric liver disease patients secondary to varying etiologies.

Method: All pediatric (< 18 years of age) patients presenting to the Pediatric Hepatology unit of tertiary care hospital were retrospectively screened and those cases, who had evidence of hepatic fibrosis (> stage 2 as per Ishak's fibrosis staging) at baseline liver biopsy followed by sequential liver biopsies later showing definite evidence of fibrosis regression (decrease in Ishak's fibrosis staging by at least 2 stages) were selected for review.

Results: A total of 9 pediatric cases encompassing three different case scenarios: autoimmune hepatitis (AIH, n=7), chronic hepatitis B infection (n=1) and budd chiari syndrome (BCS, n=1) were included in the study. In all the cases, hepatic histology showed gradual regression of liver fibrosis varying from thinning and perforation of fibrous septae allowing mingling of adjacent hepatocyte populations (in cases with baseline frank cirrhosis) to complete resolution of fibrosis (in cases with baseline early fibrosis stages) [Figure 1]. In pediatric AIH patients, these findings were also accompanied by decrease in severity of hepatic inflammation, i.e decrease in interface activity/pseudorosette formation/lymphoplasmacytic inflammation, along with a simultaneous decrease in liver stiffness (as measured by transient elastography) in almost all of the patients. Similar findings were also seen in the sole BCS patient, where centrilobular congestive changes in baseline biopsy were replaced by unremarkable hepatocytes in the follow up biopsy along with fibrosis regression.

Conclusion: To conclude, regression of cirrhosis is a well known, though still inadequately characterised phenomenon in various pediatric liver diseases. This series of 3 different pediatric liver case scenarios helps us shed light and rekindle the interest in much needed prospective studies including larger number of patients across all etiological groups targeting serial histological evaluations of liver diseases to help understand this enigmatic phenomenon.
**Legends to Figure 1**

- **Autoimmune Hepatitis Case** - 
  - Index Liver Biopsy- Figure 1(a & b) - Macronodule formation [HE stain, 40x and MT stain, 100x respectively]
  - Repeat Liver Biopsy-Figure 1(c)- Breaking septae with perforating hepatocytes (arrow) [HE, 200x]

- **Chronic Hepatitis B Infection Case** - 
  - Index Liver Biopsy- Figure 1(d) - Thick curved fibrous septae enclosing regenerative hepatic parenchyma (MT, 40x)
  - Repeat Liver Biopsy- Figure 1(e & f)- Thinned and perforated fibrous septae (MT, 40x and HE, 100x (circle) respectively]

- **Budd Chiari Syndrome Case** - 
  - Index Liver Biopsy- Figure 1(g) Evidence of Cirrhosis [HE, 100x]
  - Repeat Liver Biopsy- Figure 1(h) Disappearing septae [HE, 40x], & Figure 1(i) Perforated septae (arrow) [MT, 200x]

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Predictive risk factors and transient elastography in pediatric non alcoholic fatty liver disease in Indian population

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Objectives and Study: Limited data is available on the role of predictive risk factors in causation of pediatric nonalcoholic fatty liver disease (NAFLD), especially in Asian populations. Also, utility of transient elastography (TE) in such cases is still largely unknown. We, therefore, aimed to study the significance of parental metabolic risk factors, patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene polymorphism and TE in pediatric NAFLD.

Method: We performed an observational, prospective study in the Pediatric Hepatology unit of a tertiary care hospital including overweight/obese children (aged ≤18 years) with or without NAFLD (ultrasonography based) including and their parents. Detailed evaluation of subjects was done including metabolic screening, PNPLA3 I148M polymorphism, and TE.

Results: Final study group included 69 patients included in the NAFLD group and 30 patients in the non NAFLD group. In the NAFLD group, there was high incidence of metabolic diseases (NAFLD, dyslipidemia, metabolic syndrome etc) in the parents where more than 3/4th of the families had atleast one parent with either fatty liver (80 %) or low High Density Lipoprotein levels (84 %). Similarly there was high incidence (> 2/3rd of families) of insulin resistance, hypertension and high serum triglycerides in atleast one parent in the NAFLD group. In the NAFLD group, homozygosity (GG status) and heterozygosity (CG status) for PNPLA3 polymorphism was seen in 24 (34.8 %) and 23 (33.3 %) overweight/obese children respectively. In the non NAFLD group, only 1 (3.3 %) subject had homozygous mutation, while heterozygous status was found in 8 (26.7 %) subjects. Family history of NAFLD (in any parent), higher alanine aminotransferase (ALT) levels and higher total cholesterol levels in the child independently predicted possibility of NAFLD. Based on the logistic regression model of Pediatric NAFLD in overweight/obese children, probability of developing Pediatric NAFLD was derived by the equation: P (Y) = 1/1 + e ^ [ -7.688 + (2.935 x Family History of NAFLD in any parent) + (0.075 x ALT) + (0.045 x Cholesterol) ] where 'Family History of NAFLD in any parent' is 0 or 1 when absent or present, respectively. The above equation leads us to a probability of developing NAFLD in overweight/obese children as 92.4 % based on the sample data.

At a cut off of 259.5 dB/m, controlled attenuation parameter (CAP) measurement (by TE), could predict presence of steatosis in children with 88.4 % sensitivity and 100 % specificity and AUROC of 0.965 (95 % CI 0.931 to 1.000).

Conclusion: There is high familial incidence of metabolic diseases in the children with NAFLD. In an overweight/obese child, presence of family history of NAFLD (in any parent), and higher ALT and total cholesterol levels, independently predict presence of NAFLD. Homozygosity for PNPLA3 polymorphism in children could have a potential to be an independent predictor of pediatric NAFLD, but could not be proven in the present study. CAP can be useful as a non invasive modality to screen fatty liver in children. Large prospective studies can further strengthen the evidence to allow prognostication and better overall management.

Contact e-mail address: drvickyster@gmail.com
Autoimmune liver disease in Indian children- is it different from the Western World?

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Objectives and Study: Pediatric autoimmune liver disease (AILD), encompassing both autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC), is one of the commonest treatable liver disease. Information on its entire spectrum is lacking from the countries of the Asia-Pacific region, thus limiting the formulation of population specific guidelines. This work thus aimed to study the clinical profile, and prognosis of pediatric AILD subjects.

Method: A review of all pediatric AILD cases presenting over a 6 year (2011-2017) period was done. Diagnostic criteria for AIH included classical histological criteria with/without serum autoantibodies and/or elevated Immunoglobulin G levels. ASC was diagnosed based on features of AIH along with either abnormal cholangiographic study (multiple strictures and/or dilatations of biliary tree) or histological evidence of primary bile ductal injury (fibro-obliterative cholangitis etc).

Results: A total of 85 subjects (AIH=70 and ASC=15) were diagnosed as having AILD. Clinically, acute presentation (as acute hepatitis, acute liver failure/ALF or acute-on-chronic liver failure) was seen in one-third (35.7 %) of AIH cases, as against predominant chronic presentation (as chronic hepatitis, or compensated/decompensated chronic liver disease) in majority (86.7 %) of ASC cases. Majority of cases in both groups (73 % and 87 % respectively) had evidence of advanced hepatic fibrosis (> F4 as per Ishak's staging). Around half of the cases (43 % and 47 % respectively) had clinical evidence of hepatic decompensation, while vast majority (70 % and 100 % respectively) had evidence of portal hypertension. Seronegative AILD was seen in about one-fourth of the cases (22.9 % and 26.7 % respectively). Overall 38 (44.7 %) subjects had extrahepatic autoimmune disorders (EHADs); common ones being autoimmune haemolytic anemia/AIHA (35.3 %) and celiac disease/CD (11.8 %). Family history of autoimmune disorders was positive in seen in 9 (10.5 %) subjects. On the basis of magnetic resonance cholangiopancreatography (MRCP) in ASC subjects, large duct disease (abnormal cholangiograms) was established in 8 subjects while small duct disease (normal cholangiograms but classical histopathological picture) was seen in 7 subjects. MRCP, available in 50 % AIH subjects, also showed non-specific biliary changes in 11 (15.7 %) subjects secondary to underlying cirrhotic liver. Good outcome (survival with native liver with medically manageable disease), was seen in 80 % subjects while poor outcome (death/need for liver transplantation or LT) was seen in 13 % subjects of AIH subjects [Figure 1]. Similarly, ASC subjects had good outcome in 80 % subjects while poor outcome was seen in 20 % subjects. Survival subgroup analysis did not reveal significant differences in AIH versus ASC group; in those with or without cirrhosis; as per different types of AIH; and in seronegative versus seropositive AILD.
Conclusion: Pediatric AILDs usually present with advanced hepatic disease in our part of the world due to a late diagnosis, but may have a good outcome if timely therapy can be instituted. Seronegative AILD is a distinct entity which requires further evaluation. Patients should be carefully screened for presence of autoimmune disorders, especially AIHA and CD.

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Association of the variants rs738409 and rs2896019 in the palatin-like phospholipase 3 gene (PNPLA3) in Greek children and adolescents with fatty liver disease

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Objectives and Study: Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in children, ranging from simple steatosis to non alcoholic steatohepatitis (NASH) and cirrhosis. Genetic predisposition can play an important role in development of NAFLD. The purpose of our research was to assess the association between two polymorphic variants, rs738409 and rs2896019, in PNPLA3 gene with the presence of NAFLD in the Greek population. The study recruited 182 children and adolescents, 91 healthy subjects of normal weight (control group) and 91 subjects separated in three groups. Group A included 31 obese subjects, median age 10 years, with NAFLD or NASH. Group B included 33 obese subjects, median age 10 years, without NAFLD. Group C included 27 subjects of normal weight, median age 8 years, with NAFLD or NASH. The Ethics Committee of AUTh (Aristotle University of Thessaloniki) approved the protocol of the study.

Method: In all participants NAFLD was assessed by abdominal ultrasound and NASH by liver biopsy whereas blood samples were taken for determination of liver function. Children with known liver diseases, other than NAFLD or under lipid-lowering drugs affecting lipid metabolism were excluded from the study. Genomic DNA was isolated and SNP genotyping was performed by using a polymerase chain reaction with specific primers followed by restriction fragment length polymorphism analysis. The statistic analysis was based on the SPSS v.24 system, using the \( \chi^2 \) (Exact Significance 2-sided, based on Fisher’s Exact Test) and a p-value< 0.05 was considered statistically significant. The association of alleles and genotypes was carried out using a logistic regression analysis.

Results: The frequencies of the PNPLA3 rs738409 genotypes, CC, CG, and GG in the healthy control group were 73%, 24% and 3%, and those in NAFLD patients were 13%, 18% and 44.2% respectively, showing a higher frequency of the risk allele (G allele) in NAFLD patients (p = 0.006). Among the patients, the CG+GG genotype frequency was significantly higher in patients with NASH (p&LT; 0.001). We detected strong association between rs738409 C>G variant and NAFLD (P&LT; 0.001) or NASH (P&LT; 0.001) in Groups A and C. The presence of this SNP was extremely high (93%) in Group C patients, proving the strong relation to the pathogenesis of NAFLD even to patients with normal BMI. No association was proved between the BMI and the presence of CG or GG allele in all patients (P>0.050). The frequencies of the PNPLA3 rs2896019 genotypes, TT, GT, and GG in the healthy control group were 79%, 21% and 0%, and those in NAFLD patients were 28.5%, 25%, and 0% respectively. The frequency of GG allele was significantly low in all Groups. Only two cases, one in Group B and one in Group C were a GG allele carriers, proving no association between the risk allele (G allele) and NAFLD or NASH in Greek population (p>0.050) and no influence to the body mass or to the lipid levels.

Conclusion: Our result supported the idea that the PNPLA3 rs738409 polymorphism contributes to the susceptibility to NAFLD. No correlation of rs2896019 polymorphism with fatty liver disease was observed. Our data suggest the reasonability of including a PNPLA3 rs738409 SNP test to identify high risk groups for NAFLD in Greece.

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Concurrent extrahepatic autoimmune involvement in children with autoimmune hepatitis

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Objectives and Study: Autoimmune hepatitis (AIH) is a chronic hepatopathy, characterized by immunological activation and inflammatory activity. As with other autoimmune disorders, laboratory tests may show hypergammaglobulinaemia and circulating autoantibodies. Autoimmune diseases frequently overlap each other and several reports on the association between AIH and extrahepatic autoimmune disease (EAD) have been published in adults. Our aim was to assess the frequency of the association of AIH with EAD and the impact, if any, on the outcomes and the clinical or analytical expression of the liver disease.

Method: We selected a cohort of children with AIH through consecutive and retrospective sampling, based on the liver biopsy registry and the patient records of two referral centres. AIH diagnosis was based on the 1999 reviewed international criteria. The study period ranged from 2006 to 2017. Selected cases were screened to identify concurrent EAD through medical history revision. We took into account those potential EAD already described in relation with AIH (J Clin Gastroenterol 2010; 44:209). Several variables were compared between the groups of isolated AIH and AIH with extrahepatic autoimmune disorder: demographic characteristics, analytical parameters at the time of diagnosis, clinical presentation, severity of histological features and proportion of patients who responded properly to treatment or relapsed under immunosuppressive drugs. Binary results were reported as percentages with 95% confidence interval (95%CI) and continuous variables as median and interquartile range (IQR). The Mann-Whitney U-test was used to evaluate differences in continuous variables and $\chi^2$ test for dichotomous variables. A p-value < 0.05 was considered statistically significant.

Results: A total of 100 patients under 16 years-old with AIH were identified. Among them, 23% (95%CI 16% to 32%) were diagnosed with some type of EAD, mainly coeliac disease and ulcerative colitis (UC, 65% of the associations), but also with juvenile idiopathic arthritis, diabetes mellitus and autoimmune lymphoproliferative syndrome (ALS). In one case coexisted AIH with UC and ALS. Most of them developed AIH after being diagnosed with the EAD (83%). Table below depicts the principal analyses carried out. No significant differences were identified between the groups of isolated AIH and AIH with EAD in terms of patient characteristics, liver-related clinical outcomes or analytical results. However, statistical power for some comparisons was limited, with values around 40%.

Conclusion: In near one out of four children with AIH, there is an associated extrahepatic autoimmune compromise. There is a non-significant trend to higher relapse rates during treatment in the group of patients with AIH and EAD. Children with an EAD should be assessed for the concomitant presence of an asymptomatic AIH.
<table>
<thead>
<tr>
<th></th>
<th>Isolated AIH (77 patients)</th>
<th>AIH with EAD (23 patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>75.3%</td>
<td>60.9%</td>
<td>0.193</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>7.3 years (3.6 to 11.5)</td>
<td>9.4 years (2.5 to 12.7)</td>
<td>0.635</td>
</tr>
<tr>
<td>Median score in classical criteria (IQR)</td>
<td>12 points (10 to 15)</td>
<td>11 points (9 to 16)</td>
<td>0.173</td>
</tr>
<tr>
<td>Median GPT (IQR)</td>
<td>673 U/L (160 to 1835)</td>
<td>834 U/L (190 to 1476)</td>
<td>1.000</td>
</tr>
<tr>
<td>Median IgG</td>
<td>1570 mg/dL (985 to 2292.5)</td>
<td>1693 mg/dL (1265 to 2864)</td>
<td>0.337</td>
</tr>
<tr>
<td>Interface hepatitis</td>
<td>76.6%</td>
<td>65.2%</td>
<td>0.273</td>
</tr>
<tr>
<td>Treatment response</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Relapse</td>
<td>24.7%</td>
<td>43.5%</td>
<td>0.115</td>
</tr>
</tbody>
</table>

GPT, glutamic pyruvic transaminase; IgG, immunoglobulin G. IQR, interquartile range.

**Table**

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Objectives and Study: Pediatric cholestatic liver diseases (CLDs), including progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome (ALGS), biliary atresia (BA), and primary sclerosing cholangitis (PSC), are rare conditions and a source of high mortality and morbidity. CLDs are accompanied by symptoms that may greatly reduce quality of life. This study was designed to examine the symptoms and daily impacts on functioning of CLD through qualitative interviews with patients and their caregivers.

Method: Patients between the ages of 1 and 17 years diagnosed with CLD who experienced pruritus at least “some of the time” were enrolled in the study. Telephone interviews with caregivers were conducted for patients 1-5 years old (n=6), in-person interviews with patients and caregivers were conducted for patients 6-12 years old (n=7), and telephone interviews with patients were conducted for patients 13-17 years old (n=2). The interviews involved asking the patients and caregivers open-ended questions about the patient's experience of CLD. Patients and caregivers rated the disturbance level associated with each symptom and each functional impact on a 0-10 scale. Interviews were recorded and the transcripts were thematically analyzed using Atlas.ti. Key themes were identified through the frequency with which they were mentioned and the level of disturbance ascribed to them.

Results: Of the 15 enrolled patients, 7 were diagnosed with PFIC, 5 with ALGS, 2 with BA, and 1 with PSC. Pruritus was reported to be the most frequent and most disturbing symptom while other symptoms were much less salient (reported by < 50% of patients and caregivers). Pruritus received an average disturbance rating of 6.3, with PFIC patients and caregivers reporting the highest impact (7.8). Pruritus was reported to occur all over the body. All respondents reported that pruritus occurred most frequently at night and was also reported to occur frequently upon waking and when tired or unwell. The figure displays the frequency of functional impact reports and associated disturbance ratings. Pruritus-related sleep disturbance, including difficulty falling and staying asleep, and requiring soothing from caregivers to sleep, was the most salient impact (77% reported, average disturbance=7.6). Other commonly experienced impacts were fatigue (69%), difficulty focusing (46%), and scarring (46%). Fatigue and sleep disturbance were experienced similarly across PFIC and non-PFIC patients.

Conclusion: Pediatric CLDs cause significant pruritus that is associated with disturbed sleep. The interviews conducted in this study help to further describe the experience of pruritus and how it impacts the daily lives of patients. This qualitative information is highly important to support the development of patient-reported and observer-reported outcome instruments that can be used to evaluate treatment efficacy in clinical trials with PFIC and other pediatric CLD patients.
Disclosure of interest: K. Torfgård and J.P. Mattsson are employees of Albireo AB. P.N. Soni is an employee of Albireo Pharma, Inc.
HEPATOLOGY - General Hepatology

H-P-089

Turkish children with fibrinogen storage disease: One of them with a novel mutation fibrinogen Ankara

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Objectives and Study: Fibrinogen storage disease (FSD) is an autosomal dominant hereditary disorder characterized by hypofibrinogenemia and accumulation of abnormal fibrinogen in the liver. In here, we present seven children with FSD due to two different mutations in the fibrinogen gamma gene (FGG).

Method: FSD was diagnosed with hypofibrinogenemia, intrahepatic fibrinogen inclusions and/or description of the mutations in fibrinogen gamma gene by molecular studies. Clinical, laboratory and histopathological findings of the patients were documented.

Results: Seven patients (1 male, 6 female) diagnosed with FSD. The median age of the patients was 5.5 years old (range 1-11).

Proband 1. A 5-years-old girl was referred to our clinic for liver transplantation with diagnosis of cryptogenic cirrhosis. Hepatomegaly was incidentally first detected at 8-months-old age at a local hospital. Our patient and family members (mother, two sisters and one brother) were found to carry p.Arg375Trp mutation (fibrinogen Aguadilla) in FGG gene. Ursodeoxycholic acid (UDCA) and carbamazepine were given to our patients and her symptomatic siblings however carbamazepine had to be ceased in patients due to elevated gamma-glutamyl transferase levels.

Proband 2. 2 years-old girl presented with elevated transaminase levels. Fibrinogen Aguadilla mutation was detected in the patient and her mother. UDCA was given to the patient.

Proband 3. 5.5 years-old girl was presented with elevated transaminase levels. A novel mutation named as fibrinogen Ankara (c.1096C>G; p.His340Asp) was detected in the patient and her father. Transaminase levels were decreased spontaneously in the follow-up period, no medication was needed.

Hypolipoproteinaemia was detected in probands with fibrinogen Aguadilla mutation. The clinical and laboratory findings of the patients were shown in the table 1.
<table>
<thead>
<tr>
<th></th>
<th>Family I with f Aguadilla mutation</th>
<th>Family II with f Aguadilla mutation</th>
<th>Family III with f Ankara mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>Proband I 7/Female</td>
<td>Sister I 1/Female</td>
<td>Sister II 5/Female</td>
</tr>
<tr>
<td></td>
<td>Sister III 9/Female</td>
<td>Brother 11/Male</td>
<td>Proband II 2/Female</td>
</tr>
<tr>
<td></td>
<td>Sister II 5/Female</td>
<td>Proband III 5.5/Female</td>
<td></td>
</tr>
<tr>
<td>Organomegaly</td>
<td>Hepatomegaly</td>
<td>Hepatomegaly</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>AST/ALT, IU/L (N, 10-40 IU/L)</td>
<td>411/223</td>
<td>106/65</td>
<td>111/170 40/44 23/18 77/151 50/42</td>
</tr>
<tr>
<td>GGT, IU/L (N, 10-32 IU/L)</td>
<td>333</td>
<td>105</td>
<td>39 25 22 67 24</td>
</tr>
<tr>
<td>Total and direct bilirubin,</td>
<td>5.6/3.1</td>
<td>0.8/0.01</td>
<td>0.7/0.05 0.6/0.02 0.8/0.1 0.6/0.1</td>
</tr>
<tr>
<td>mg/dl (N, &lt;1 mg/dl)</td>
<td></td>
<td></td>
<td>0.5/0.05</td>
</tr>
<tr>
<td>Prothrombin, sec. (N, 10-14</td>
<td>17</td>
<td>15.9</td>
<td>17.3 15.5 13 14.8 14</td>
</tr>
<tr>
<td>sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dl (N, 200-</td>
<td>52</td>
<td>25</td>
<td>55 107 147 74 75</td>
</tr>
<tr>
<td>400 mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver histology</td>
<td>Moderate-severe fibrosis, cirrhosis,</td>
<td>Steatosis, mild fibrosis, intrahepatic fibrinogen inclusions</td>
<td>Mild, moderate fibrosis, intrahepatic fibrinogen inclusions</td>
</tr>
<tr>
<td></td>
<td>intrahepatic fibrinogen inclusions</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steatosis (75%), no fibrosis, intrahepatic fibrinogen inclusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td>Steatosis (20%), no fibrosis, intrahepatic fibrinogen inclusions</td>
</tr>
</tbody>
</table>

|Table 1|

**Conclusion:** FSD is an endoplasmic reticulum storage disease like alpha 1 antitrypsin deficiency. The clinical presentation varies from advanced liver fibrosis to asymptomatic hypertransaminasaemia and hypofibrinogenemia. Although it has been showed that UDCA and carbamazepine might be useful in patients with FSD, it is necessary to evaluate adverse effects of carbamazepine therapy and therapeutic response in patients with FSD.

**Keywords:** Fibrinogen storage disease, fibrinogen gamma gene, child, cirrhosis

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Wilson disease in children: a 17-year follow-up study

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Introduction: The aim of this study, is examination of the clinical characteristics, laboratory results and treatment responses of Wilson’s disease patients.

Patients and methods: This study was conducted in Sisli Etfal Hospital, a tertiary care institution in Istanbul, Turkey. Between 2000 and 2017, 41 children between 5 and 18 years of age with Wilson’s disease diagnosis in the child gastroenterology department were recorded retrospectively from the file records. Hepatic enzymes, serum copper, ceruloplasmin, copper levels in 24 hour urine, histopathological evaluations of liver biopsies and kayser-fleischer ring, dry weight of liver copper were investigated.

Results: The study included 20 female and 21 male wilson patients with a mean age of 10±1.5 years (min:5-max:18). %68 of families had consanguineous marriage and %38 had first-degree consanguinity. Most of the cases (37 cases) were hepatic Wilson (5-15 years) and 4 cases were neurorowilson (10-15 years). Twenty cases (49%) were presented with chronic hepatitis, 10 cases (24%) with acute hepatitis, 6 cases (15%) with chronic hepatitis with portal hypertension and 5 cases (12%) with fulminant hepatitis clinic.

The presenting manifestations of the disease were as follows: abdominal distantion 19 of 41 (%46), jaundice in 11 of 41 patients (27%) , epistaxis in 4 of 41 (9%) , ascites in 1 of 41. There were no symptoms in 16 patients (%40), liver enzymes were elevated in coincidental blood tests. Hepatosplenomegaly was the most common clinical finding, in 15 of 41 patients (38%), followed by jaundice in 8 of 41 (37%) , hepatomegaly in 6 of 41 (%15). There were no clinical findings 11 patients (%27). K-F rings were present in 7 % of the patients (%18). Three patients with neurological symptom had K-F rings. Laboratory findings of the disease were as follows: raised transaminases in 31 of 41 patients (78 %), hyperbilirubinemia in 10 of 41 (%25) , prolonged prothrombin time in 4 of 41 (10%) , acute Coombs-negative hemolytic anemia in 4 of 41 (10%) , hypoalbuminemi in 4 of 41 (10%). The mean serum copper level was 88,8 ug/dl , and the mean serum ceruloplasmin was 15,1 mg/dl.

24-hour urinary copper excretion was 488 ug.

All 41 patients were submitted to an abdominal ultrasound. Liver copper content was determined in only 35 patients, and mean of dry weight copper is 443 mcg/gr. Patients with hepatic symptoms were treated with D-penicillamine and zinc sulfate. Patients with neurological symptoms were treated with trientin and zinc sulfate. The mean of the patients follow-up period was 9±1.2 years . Liver function test results became normal after a mean period of 12±1.1. Mean of urinary copper excretion after penicillamine treatment was 138 mcg/24 hours.

Liver transplantation was indicated in three patients who developed chronic progressive liver failure after 5 years

Discussion: This report presents the clinical manifestations and laboratory findings of WD in children and underlines the difficulties in establishing the diagnosis in a pediatric population.

Wilson’s disease is a rare genetic but treatable metabolic disorder which has a favorable prognosis when diagnosed early and treated adequately.

Measurement serum ceruloplasmin levels and determination of 24-hour urinary copper excretion are important for patients with raised transaminases.

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Systematic literature review of the effect of partial external biliary diversion surgery on clinical and biochemical outcomes in progressive familial intrahepatic cholestasis patients

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Objectives and Study: Data are limited on the impact of partial external biliary diversion (PEBD) surgery on clinical outcomes in patients with progressive familial intrahepatic cholestasis (PFIC). We performed a systematic literature review of PEBD in patients with any PFIC subtype to evaluate the relationship between potential biomarkers and early response (eg, relief of pruritus) or long-term outcomes (eg, need for liver transplant [LTX]).

Method: Searches identified 150 publications before November 2016, of which 16 met inclusion criteria. Correlation analysis of changes in biomarkers and clinical outcomes was performed; partial responders were added to non-responders. Receiver operating characteristic (ROC) analysis was used to identify cut-offs, which provided optimal sensitivity and specificity.

Results: The 16 studies included an aggregate of 155 PFIC patients. Of these, 104 (67%) demonstrated an early clinical response to PEBD, 14 (9%) a partial response, and 37 (24%) were non-responders. Most data were aggregate; individual patient data were reported for serum bile acids (n=42), bilirubin (n=31), and ALT (n=28). Prior to surgery, bile acids were 25-35 times >ULN (mean: 322 µmol/L). Reduction in bile acids post-PEBD correlated with positive early clinical outcomes with high sensitivity and specificity (area under the curve [AUC], 0.99; p< 0.0001; figure). Baseline bilirubin levels were typically 5-8 times >ULN (mean: 94 µmol/L); however, variability was high and levels were close to normal in several patients. Reduction in bilirubin levels post-PEBD correlated with positive early clinical outcomes with good sensitivity and specificity (AUC, 0.87; p=0.003). Baseline ALT levels were typically 1-4 times >ULN (mean: 168 U/L) and were highly variable. ALT reductions did not significantly correlate with early positive clinical outcomes (AUC, 0.74; p=NS). Based on 3 studies with available data, reductions in bile acids and bilirubin but not in ALT levels were independently highly associated with decreased aggregate need for LTX after PEBD.

Conclusion: Changes in serum bile acids and bilirubin seem useful as biomarkers in predicting both early and long-term outcomes after PEBD and could presumably be utilized for the same purpose when evaluating pharmaceutical intervention in PFIC patients.
[ROC curve of serum bile acid levels post-PEBD surgery and early clinical response.]

Disclosure of interest: HJV is a consultant for Albireo, Ausnutria Hyproca, Friesland Campina Dairy Foods, and Danone/Nutricia Research. RJT is a consultant for Albireo, Shire, Alexion, Arcturus, Retrophin, GSK, and Qing Bile Therapeutics. HA is a consultant for Albireo, Alexion, and Baxter. BF is a consultant for Albireo and received travel support from AbbVie. EL is a former employee of Albireo. PGG, JPM, KT, and PNS are employees of Albireo.
Changing scenery of chronic hepatitis in children over two decades - how a Paediatrics Department from Bucharest tells the story

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Objectives and Study: Chronic hepatitis, regardless of cause, results in significant morbidity and has a high impact on patients' quality of life, especially when the onset is as early as childhood. The purpose of this study was to assess the etiologic diagnosis in chronic hepatitis, how this varied over time and in terms of epidemiologic characteristics over a period of two decades.

Methods: We conducted a retrospective study, reviewed the medical records of children with chronic hepatitis evaluated in the Paediatrics Department of „Grigore Alexandrescu” Emergency Children’s Hospital, between 1997 and 2016 and analyzed etiologic diagnosis, gender, age at diagnosis and family history.

Results: We identified 829 cases of chronic hepatitis, 55 were excluded due to incomplete data. We analyzed a cohort of 774 patients. The etiology was: viral hepatitis (B±D or C), Wilson Disease, autoimmune hepatic disease, toxic hepatitis in 86, 4, 3.6, 2.3%. For viral hepatitis, the etiology was hepatitis B virus in 87.5%, almost a quarter of these patients having hepatitis D coinfection, and hepatitis C virus in 12.5%. NASH, chronic hepatitis in metabolic diseases and congenital biliary pathology were diagnosed in less than 2% each. Between 1997 and 2006, 99% of the etiologic diagnoses recorded were viral infections. Due to increased awareness and the enrichment of diagnostic tools, in the interval 2007-2016, a third of etiologies (35.5%) were non-viral. The boys predominated in the cohort (58.7%) and across most of the etiologies (percentages over 60%) except among patients with autoimmune hepatic disease and toxic hepatitis, where the lead was taken by girls (73.1 and 77.8%). More than half of the patients were diagnosed with chronic hepatitis between 3 and 12 years. For each etiology the patients were divided in four groups according to the age at diagnosis (&LT; 1 year, 1-3 years, 3-12 years, >12 years). All patients with congenital biliary pathology and half with metabolic disease were diagnosed below 3 years, but none with Wilson Disease and only 13% with autoimmune hepatic disease. For half of the viral chronic hepatitis and the majority of toxic hepatitis (83.3%) the diagnosis was set between 3 and 12 years. The family history revealed an infected relative in a third of the cases of viral hepatitis, a positive family history in a quarter of patients with NASH, but was only positive in 3.5% for autoimmune disease.

Conclusions: In the late 1990-early 2000, viral hepatitis was almost the only etiology of chronic hepatitis we have records for in our Paediatrics Department in Bucharest. It was diagnosed predominantly between age 3 and 12. Since then, vaccination against hepatitis B was introduced and diagnostic tools became readily accessible. So the following decade changed the face of chronic hepatitis in our clinic. We predict this trend will be maintained on an ascending curve over the next years.

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Correlation between Fibroscan and MRI T2* to estimate degree of hepatic iron overload in thalassemia major patients

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Objectives: Hepatic iron overload is an important cause of morbidity and mortality in patients with thalassemia major. Current guidelines suggest serum ferritin every three months and annual magnetic resonance imaging transverse relaxation time (MRI T2*) to monitor hepatic iron load. MRI T2* is expensive and is not easily available. We investigated the correlation between MRI T2* and Fibroscan (Transient Elastography) to assess the degree of hepatic iron overload.

Method: 50 patients with thalassemia major >12 years were enrolled into this prospective cross-sectional study. Patients with chronic viral hepatitis were excluded. All patients underwent routine blood investigations, Fibroscan, Liver 1.5 Tesla MRI T2* and serum ferritin level. Fibroscan was done within 3 months of MRI T2*. The correlation between Fibroscan, MRI T2* and ferritin levels was determined using spearman correlation test and linear regression analysis.

Results: 27(54%) patients were male and 23(46%) were female. Mean age was 22.7 ± 6.5 years and serum ferritin 2396 ± 1660ng/ml. Median SGPT and SGOT were 32.5(range:16-120IU/L) and 25(11-224IU/L). Median Fibroscan and MRI T2* readings were 6.35(2.7-36.3milliseconds) and 4.87(1.7-13.7kPa) respectively. Based on MRI T2*, 11(22%), 32(64%) and 7(14%) patients had no, mild and moderate iron overload respectively. A moderate inverse correlation was seen between serum ferritin and MRI T2* readings (r=-0.51, p<0.001) and a moderate positive correlation between serum ferritin and Fibroscan readings (r=0.5, p<0.001). A weak inverse correlation was seen between MRI T2* and Fibroscan (r=-0.27, p=0.06). AUC for Fibroscan to detect mild and moderate iron overload was 0.60 (CI:0.43-0.78) and 0.71(CI:0.44-0.99) respectively. Fibroscan value >6.3kPa predicted mild to moderate iron overload with sensitivity and specificity of 56.4 % and 72.7 % respectively.

Conclusion: Fibroscan and MRI T2* showed weak correlation. Larger studies are required to validate the use of Fibroscan for estimating degree of hepatic iron overload.

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Role of Aspartate aminotransferase-to-platelet ratio index (APRI), GGT and platelet count in predicting severity of liver fibrosis in children with Extrahepatic Biliary Atresia

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Objectives and Study: This study analyzed the role of Aspartate aminotransferase-to-platelet ratio index (APRI), GGT and platelet count in predicting severity of fibrosis of liver in children with Extrahepatic biliary atresia.

Methods: Demographic, clinical, laboratory parameters including blood counts, bilirubin, SGOT, SGPT, ALP, GGT and liver histological features were prospectively determined in 77 children with biliary atresia between 2012 and 2017. Liver biopsies were done in all children for diagnosis and staging of fibrosis. They were staged according to ISHAK fibrosis staging. The correlation lab parameters (APRI, GGT, Platelet count) and degree of fibrosis on liver biopsy was determined using spearman correlation test.

Results: The median age at presentation was 75 days (22-390 days). 28 (36.4 %) were female and 49 (63.6 %) were female. A moderate positive correlation was seen between age of presentation and degree of fibrosis on liver biopsy (r=0.4, p=0.000). Age of more than 70.5 days predicted fibrosis stage 5 or more with a sensitivity of 75% and specificity of 55%. We found moderate correlation between APRI and degree of fibrosis (r=0.34, p=0.007). APRI of more than 1.03 had a sensitivity of 76 % and a specificity of 45% to predict fibrosis ISHAK stage 5 or more. We also moderate inverse correlation between platelet count and degree of fibrosis (r= - 0.35, p=0.002). Platelet count of less than 3.5 lacs had a sensitivity of 74% and specificity of 56 % to predict fibrosis of stage 5 or more. No significant correlation was found between levels of GGT, total serum bilirubin, SGOT, SGPT, ALP, Serum albumin and degree of fibrosis.

Conclusion: Trends of lab parameters such as platelet count and APRI may help in predicting the degree of fibrosis in children with biliary atresia. Further large scale studies are needed to develop non invasive scoring systems for assessing the degree of liver fibrosis in children with biliary atresia.

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Causes of infantile acute liver failure in the West of Scotland

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Introduction: Fulminant acute liver failure is a rare event in infants. It is defined as a hepatic based coagulopathy, with evidence of liver injury, in the absence of established liver disease. It does not require the presence of encephalopathy. The data defining the aetiology and incidence of liver failure originates from regional liver units. This may introduce selection bias and not provide a true reflection of the aetiology or extent.

Aims and Objectives: The aim of this study is to examine all the coagulation screens performed in our centre and identify those that fit our current definition of acute liver failure. By reducing the impact of bias we are able to more accurately define the aetiology and characteristics of liver failure in infants.

Subjects and Methods: All of the coagulation screens performed at the Royal Hospital for Children, Glasgow between June 2015 - June 2016 were examined. The inclusion criteria were infants aged less than 1 year with a prothrombin time greater than 18 seconds, not corrected with vitamin K, associated with evidence of liver injury. The notes of these patients were then retrospectively reviewed.

Results: Over the year, 9989 coagulation screens were performed. 669 tests were from 155 individuals less than one year old with a PT greater than 18 seconds. Results showed 24 out of 155 (14%) had a hepatic based coagulopathy. The aetiologies of these patients included hypoxic ischaemic encephalopathy (33%), ischaemic insult (54%), neonatal haemachromatosis (4%), metabolic disease (4%) and paracetamol toxicity (4%). 75% of patients survived while 25% patients died without liver transplant. None underwent liver transplantation or transfer to a regional liver unit; this is due to either spontaneous recovery or death prior to transfer. 120 patients were identified with a non-hepatic-based coagulopathy. Of these patients 63 (53%) were post-operative results, mainly from cardiac by-pass surgery, 14 (11%) were ECMO patients, 19 (15%) severe sepsis, with a further 23 (19%) other aetiologies. 10 premature patients were identified and excluded due to a lack of normative reference ranges.

Summary: The aetiology of infant liver failure is currently defined by data from regional liver units. This study identified several infants in fulminant hepatic failure who would not be included in this data due to death prior to transfer. Expanding this format to include a greater age range and time scale will help more fully define the cause and characteristics of patients with acute liver failure in the west of Scotland.

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Is there an increased risk of liver steatosis in children with type 1 diabetes mellitus?

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Objectives and Study: Adult patients with type 1 diabetes mellitus (DM) are at an increased risk for non-alcoholic fatty liver disease (NAFLD). At present NAFLD detection is based on ultrasound (US) and elevated levels of ALT. Due to limited sensitivity of this assessment we applied transient elastography of FibroScan® with option Controlled Attenuation Parameter (CAP). The aim of our study was to find out whether pediatrics patients with type 1 DM have liver steatosis in FibroScan® measurements and compared the results with overweight/obese patients. As recent studies in large pediatric population assessing hepatic steatosis in children using different tools and FibroScan® with CAP found that optimal threshold to detect steatosis is CAP > 249 dB/m with sensitivity 72% and specificity 98%.

Method: In all groups of patients (type 1 DM, overweight/obese and lean control) NAFLD was primarily excluded based on normal US and ALT value. We used liver steatosis measurements by FibroScan® with CAP option for more precise assessment of hepatic steatosis and stiffness of the liver in 3 groups of patients matched for age (age 8-18 years). The anthropometric measurements (BMI, waist and chest circumference) and body composition (BC) like lean body mass (LBM) and adipose tissue (AT) were also done in type 1 DM and overweight/obese patients. We analyzed 37 patients with type 1 DM, 43 patients with overweight/obesity and 21 lean controls. For group comparison we used Mann-Whitney U test and Kruskal-Wallis test and simple linear regression for correlation analysis.

Results: There were no differences in age among groups overweight/obese patients and with type 1 DM (median age 13.4 yrs vs 14.1 yrs). The control group was slightly younger (median age 12.1 yrs). The median steatosis measured by CAP in group overweight/obese patients was significantly higher - 242 dB/m (range 126-400) than in patients with type 1 DM - 202 dB/m (range 102-318) and controls - 200 dB/m (range 132-261) (p<0.05). There were no significant difference between patients with type 1 DM and controls (p=0.9393). There were no significant difference in liver fibrosis (E) measured by FibroScan® between all groups. Median SDS BMI in overweight/obese patients was 1.98 (range 1.21-3.26), in type 1 DM patients - 0.06 (range -2.26 - 2.23) and in controls median was -0.55 (range -2.26 - 0.77). In children with type 1 DM CAP values correlated with age and all anthropometric parameters (BMI, waist circumference, %LBM and %AT) (r² range 0.12 to 0.16, p<LT; 0.05). There were no significant correlation comparing E values with this parameters (p>0.05). 28% (12/43) patients with overweight/obesity, 19% (7/37) patients with type 1 DM and 9.5% (2/21) controls received CAP>249 dB/m using FibroScan® which is suspected to be early stage of liver steatosis.

Conclusion:
- Children with type 1 DM do not indicate a significantly increased prevalence of NAFLD compared to lean controls
- Increased risk of liver steatosis in children with type 1 DM is associated with unfavourable anthropometric factors

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PORTAL HYPERTENSION IN CHILDREN: EXPERIENCE OF A TERTIARY CENTER IN TURKEY

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OBJECTIVES AND STUDY: To evaluate the aetiology, clinical presentation, therapy and prognosis in children with portal hypertension (PH).

METHOD: We conducted a retrospective analysis of children diagnosed with PH at our institution between 1.1.1998 and 31.12.2016. Clinical, laboratory, radiologic findings, therapies and complications of the patients were obtained from the medical records.

RESULTS: 222 patients [(median age, 77 months (IQR; 1.5 months-7.8 years)] were diagnosed with PH, 60% of whom were male. Among the patients, 131 were in cirrhotic group (126; intrahepatic-sinusoidal type and 5; post-hepatic type) and 91 were in non-cirrhotic group (45; pre-hepatic type, 45, intrahepatic-pre-sinusoidal type and 1, post-hepatic type). Clinical and laboratory findings of the cirrhotic and non-cirrhotic group were shown in table 1.

<table>
<thead>
<tr>
<th></th>
<th>Cirrhotic group (n=91)</th>
<th>Non-cirrhotic group (n=131)</th>
<th>p</th>
<th>Cirrhotic group (n=91)</th>
<th>Non-cirrhotic group (n=131)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>72 (54.9)</td>
<td>61 (67)</td>
<td>&gt;0.05</td>
<td>Hypoalbuminemia (%)</td>
<td>17 (13.4)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Age on admission, month (median (IQR))</td>
<td>24 (6-120)</td>
<td>96 (35-167)</td>
<td>&lt;0.001</td>
<td>Increased PT (%)</td>
<td>68 (53.5)</td>
<td>29 (33.7)</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>111 (84.7)</td>
<td>34 (37.8)</td>
<td>&lt;0.001</td>
<td>Ascites (%)</td>
<td>25 (19.1)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>120 (91.6)</td>
<td>80 (88.9)</td>
<td>&gt;0.05</td>
<td>Oesophageal varices (%)</td>
<td>59 (67.8)</td>
<td>84 (96)</td>
</tr>
<tr>
<td>Spleen size in US, Z score (median (IQR))</td>
<td>4.5 (2.4-5.2)</td>
<td>5.1 (3.3-7.2)</td>
<td>0.022</td>
<td>Variceal haemorrhage (%)</td>
<td>19 (14.5)</td>
<td>56 (61.5)</td>
</tr>
<tr>
<td>Leukopenia (%)</td>
<td>18 (14.1)</td>
<td>34 (37.8)</td>
<td>&lt;0.001</td>
<td>Hepatopulmonary syndrome (%)</td>
<td>8 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>68 (53.1)</td>
<td>69 (76.7)</td>
<td>&lt;0.001</td>
<td>Hepatic encephalopathy (%)</td>
<td>7 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertransaminasemia (%)</td>
<td>112 (88.2)</td>
<td>38 (42.7)</td>
<td>&lt;0.001</td>
<td>Hepatorenal syndrome (%)</td>
<td>2 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperbilirubinemia (%)</td>
<td>83 (65.4)</td>
<td>13 (14.8)</td>
<td>&lt;0.001</td>
<td>Portal biliopathy (%)</td>
<td>0</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

[Table 1]

Patients in the cirrhotic group were admitted to the hospital earlier than patients in the non-cirrhotic group (p< 0.001). The frequency of oesophageal varices and variceal haemorrhage was found to be higher in non-cirrhotic group than in cirrhotic group (p< 0.05). The frequency of hepatopulmonary syndrome, hepatic encephalopathy and ascites was found to be higher in cirrhotic group than in non-cirrhotic group (p < 0.05).

Propranolol was given to all patients in whom oesophageal varices were demonstrated by endoscopy.
Endoscopic treatments and shunt surgery were performed more frequently in the non-cirrhotic group (p< 0.001), while liver transplantation was performed more frequently in the cirrhotic group (p< 0.001). The mortality rate in the cirrhotic group (9.2%) was found to be higher than the non-cirrhotic group (5.5%), however there was no statistically significant difference (p>0.05).

**Conclusion:** In patients with non-cirrhotic portal PH, oesophageal varices, variceal haemorrhage, and complications due to hypersplenism are more frequent, while hepatic insufficiency and hepatic damage are more common in cirrhotic patients. In cirrhotic patients, liver transplantation is the optimal treatment for patients with PH. In non-cirrhotic patients, portosystemic shunts are a successful treatment option in patients who do not respond to medical and endoscopic treatments. The prognosis is worse in cirrhotic patients than non-cirrhotic patients.

**Keywords:** Child, portal hypertension, cirrhosis, oesophageal varices

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Distinct microbiota in primary sclerosing cholangitis with inflammatory bowel disease and primary biliary cholangitis

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Objectives and Study: The pathogenesis of autoimmune cholestatic liver diseases, including primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), is thought to be multifactorial and involves progressive liver injury from toxic accumulation of endogenous bile acids. In this pilot study, we aimed to identify differences in the intestinal microbiome between patients with IBD alone, PSC-IBD, PBC and healthy controls. Recently, the intestinal microbiome has been implicated in playing a role in metabolic and immune responses, suggesting a bidirectional relationship between the intestinal microbiome and bile acids. In addition, the strong association of PSC with inflammatory bowel disease (IBD) and the use of antimicrobial agents in the treatment of both IBD and PSC raises the question of the role of the gut-liver axis in either the development or progression of PSC.

Methods: Stool samples were collected (using a home commode collection kit) and metadata obtained from 60 study participants, including 16 PBC patients, 20 PSC-IBD patients with either ulcerative colitis (UC, n = 13) or Crohn's disease (n = 7), 12 IBD only patients with either UC (n=6) or Crohn's (n=6), and 12 healthy controls. Stool samples were frozen at -80°C without preservatives. Amplicons of the V4 region of 16s rRNA were sequenced on an Illumina MiSeq platform. Sequences were joined, denoised, filtered for chimeras, and clustered into OTUs (at 97% similarity). OTUs were classified against a curated database derived from GreenGenes, RDPII and NCBI. Statistical analysis was performed using the scikit-learn library and Python scripts.

Results: As expected, the intestinal microbiota (genus level) differed in patients with PBC compared to controls (Figure 1a) and in patients with PSC compared to controls (Figure 1b). However, the intestinal microbiota patients differed in composition between PBC and PSC (Figure 1c). Combining the analysis from all study participants demonstrated that the microbiome of PSC-IBD patients was most similar to the microbiome of patients with UC (Figure 1d).
Conclusions: This pilot study demonstrates that the composition of the intestinal microbiota in patients with PSC-IBD and PBC differs from each other and from healthy controls. Microbiota in patients with PSC-IBD is similar to the microbiome in individuals with UC alone. Identification of specific taxa that are responsible for the distinctions, might provide evidence for perturbations in the microbiome of patients with IBD that trigger hepatic inflammation. Further characterization of distinct microbial profiles may identify novel therapeutic targets or biomarkers.

Disclosure of interest: HS Winter serves on board of Pediatric IBD Foundation, Camp Jabberwacky and Data and Safety Monitoring Boards for Crestovo and Janssen; acted as consultant for Avaxia, Abbvie and Shire; received research grants from Abbvie, the Autism Research Foundation, Pfizer, Janssen, Nestlé, Nutricia, Pediatric IBD Foundation, Shire, Women's Wellness Institute and UCB; received royalties from UpToDate®. CJ Moran receives royalties from UpToDate® and New England Journal of Medicine.

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Neurotensin contributes to liver disease in paediatric patients onset intestinal failure via regulating the systemic bile acid homeostasis

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Objectives and Study: Intestinal failure (IF)-associated liver disease (IFALD) contributes to significant morbidity and mortality in pediatric IF patients. However, the pathogenesis of IFALD is partly understood. Here we investigate the roles of altered neurotensin (NT) in the pathogenesis of IFALD.

Methods: The ELISA was used to measure serum levels of NT in pediatric IF patients and matched healthy controls. Liver injury and fibrosis were determined by histological analysis. The bile acid (BA) contents in serum, liver and faeces were measured by ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS).

Results: It found the systemic BA compositions were altered in pediatric IF patients, as reflecting by the unconjugated primary BA increased in livers and serum, and the conjugated primary BA increased in faces. In IF patients, the serum NT levels decreased significantly, and were conversely correlated with liver enzymes (ALP, r=-0.29, p=0.03; ALT, r=-0.23, p=0.07) and markers of cholestasis (Total bilirubin, r=-0.23, p=0.08; Conjugated bilirubin, r=-0.27, p=0.04). Using in vitro and in vivo functional studies, we found that NT stimulated conjugated primary BA absorption in the ileum by increasing expression of the apical sodium-dependent bile acid transporter (ASBT).

Conclusion: Taken together, altered NT contributes to IFALD in paediatric patients through regulating the systemic bile acid homeostasis.

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HEPATOLOGY - General Hepatology

H-P-100

Characteristics and outcomes of Autoimmune Hepatitis from a tertiary paediatric Centre, Cape Town, South Africa

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Objectives and Study: Autoimmune hepatitis (AIH) is a chronic progressive immune mediated liver disease, characterized by good response to treatment. There is a paucity about its profile exist in Sub-Saharan Africa. We aimed to describe the characteristics and outcomes of children with AIH from a paediatric centre in South Africa.

Method: Between 2005-2015 thirty-nine children diagnosed with AIH at Red Cross War Memorial Children's Hospital (RCWMCH) were included. Ethical approval obtained from the University of Cape Town/RCWMCH. Relevant patient's data was retrieved from the hospital's medical records and databases. Data was analyzed using SPSS version 24.0. (p value &LT; 0.05).

Results: Most were female 74.4% (29/39), the mean age at presentation was 7.3 ± 3.4 years. Jaundice (90%) and hepatomegaly (85%) were the chief presenting symptom and sign respectively. The common mode of presentation was acute hepatitis (66.7%). Screening for standard autoantibodies was done for 35, AIH-1 diagnosed in 20/35 (57%), AIH-2 in 3% and fourteen patients (40%) were sero-negative. Out of the 25 who had MRCP 68% had associated overlap syndrome with sclerosing cholangitis. There is no difference between Autoantibody positive and autoantibody negative patients regarding patient’s characteristic and treatment outcome. Remission rate was 80%.

On long-term follow-up (mean time 4.5 ± 2.4 years): twenty patients sustained their remission; eleven patients relapsed (rate was 35%); six patients continued had partial remission; one required liver transplantation; one demised. Survival with native liver was 95%.

Albumin level, transaminases, platelets count, cirrhosis, age at diagnosis were significantly associated with outcomes (p value &LT; 0.05).

Conclusion: AIH responds well to therapy with good survival. Hence it should be considered in the work up of any child with hepatitis to apply therapy timeously to save lives.

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Objectives and Study: Hepatic dysfunction (HD) is associated with poor prognosis in critically ill patients. This study investigated the incidence of early liver dysfunction and its relationship with probable predictive variables in patients admitted to Pediatric Intensive Care Unit (PICU).

Method: This study was conducted prospectively in a 10-bed medical PICU at Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, between April and October 2013. Study group included 149 patients aged 1 month to 18 years, without chronic liver diseases and hepatitis with viral, pharmacological, and toxic origin. Patients who died 6 hours after admission or had re-admission were also excluded from the study. Liver aminotransferases levels, Total bilirubin, direct bilirubin and international normalized ratio were checked in 24, 48, and 96 hours after admission. Univariate and multivariate logistic regression were applied to fit the final model.

Results: In total, on the first day of admission, abnormal Alkaline phosphatase level was the most (66.9%) and Direct bilirubin the least (9.1%) common abnormality. At the same time, abnormal levels of all tests except Alkaline phosphatase were predictive of increased mortality (P&LT; 0.05). They remained significant even after adjusting for PRISM III score. After 48 and 96 hours, abnormal aminotransferases, International normalized ratio, total bilirubin and direct bilirubin were still remain significantly in the final model to prediction of mortality (P&LT; 0.05). On the first 24 and 48 hours of admission, a significant relationship was found between aspartate aminotransferase (P=0.001) and alanineaminotransferase (P=0.01 and P=0.04 respectively) levels and PICU length of stay.

Conclusion: Findings of the current study demonstrated that elevation of liver enzymes may predict mortality and increase PICU length of stay in critically ill children.
Liver enzymes changes in patients with acute lymphoblastic leukemia treated with Methotrexate; first report from Iran

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Objectives and Study: A number of patients suffering from acute lymphoblastic leukemia (ALL) who were being treated with Methotrexate (MTX) have referred to gastroenterologists with liver problems. Therefore, we aimed to study the level of changes in liver enzymes caused by MTX in such patients to offer a treatment protocol to prevent liver damage.

Method: In this study, a cohort was done for children who were under treatment for ALL in the Oncology Ward of Shiraz University of Medical Sciences, Shiraz, in Southern Iran. The liver function test was done before treatment and every three months after starting treatment with MTX. If the liver enzymes increased over twice the normal level, liver biopsy was done for the patients. The patients’ demographic characteristics and test results were recorded in a questionnaire.

Results: 50 patients with an age range of 1 to 16 years were studied. Based on their BMI, 12% were obese, 16% overweight, 48% normal and 24% underweight. The MTX blood level was at the therapeutic level in 23 children, under the therapeutic level in 16 children and above the therapeutic level (toxic) in 11 children. These 11 (22%) children who had increased liver enzymes (more than twice the normal level) underwent liver biopsy. There was a significant relationship between liver enzyme elevation and BMI increase. However, this was not true after increased serum MTX levels.

Conclusion: We suggest that a protocol be made so that patients being treated with MTX could be checked for elevated liver enzymes and undergo biopsy if detected to have increased liver enzyme levels and be treated by medications such as Ursobil.
Correlation between autonomic nervous system dysfunction and Wilson's disease in children; a Southern Iranian experience

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Objectives and Study: Wilson's disease is an autosomal recessive disorder which is associated with hepatic involvement, and degenerative changes in brain and Kayser-Fleischer ring of the cornea. Early involvement of basal ganglia and brainstem in Wilson's disease could lead to dysfunction of autonomic nervous system (ANS) before the patient becomes symptomatic. We evaluated the relationship between the disease severity and ANS dysfunction in affected patients.

Method: This study was conducted during 2015-2017 in two pediatric gastroenterology clinics in Shiraz, southern Iran. All the patients under 18 years of age, who referred to the mentioned clinics were included. We evaluated cardiovascular ANS function, including changes in heart rate and blood pressure after performing Valsalva maneuver, tilt test, and cold pressor test. P value< 0.05 was considered statistically significant.

Results: In this study, 31 patients with Wilson's disease were assessed. The mean (±SD) age of the patients was 12 years (±2.3, range: 1-17).Cardiovascular ANS function in the patients was significantly-affected compared with normal values (P<0.05). The correlation between Wilson's index and some of the indices of cardiovascular ANS function was not statistically significant

Conclusion: Wilson's disease scoring system cannot be beneficial in predicting patients' autonomic system outcome.
Relationship of small bowel bacterial overgrowth with metabolic and liver structural changes in children with nonalcoholic fatty liver disease

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Objectives and Study: To assess the influence of the small bowel bacterial overgrowth (SIBO) on the course of nonalcoholic fatty liver disease (NAFLD) in children. The study included 90 patients aged 5 to 17, boys - 54 (60%), girls - 36 (40%). The average age of patients was (12.08 ± 2.71) years. All patients and their parents had given their agreement to participation in the study.

Method: The presence and degree of hepatic steatosis were determined by transient elastography using «FibroScan®502-touch» with the measurement of controlled attenuation parameter. For the diagnosis of the SIBO a hydrogen breath test with glucose loading was performed using Gastrol yzer® (Bedfont Scientific Ltd, UK). We performed ELISA kit for measurement of plasma insulin levels with calculation of HOMA1-IR. We performed blood analysis with determination of erythrocyte sedimentation rate (ESR), level of platelets, aspartate aminotransferase level with determination of aspartate aminotransferase to platelet ratio index (APRI). According to the presence of steatosis and the presence of obesity/overweight all patients were divided into 3 groups: 1 group consisted of 45 patients with liver steatosis and overweight/obesity (50.0%), group 2 - 35 patients without liver steatosis with overweight/obesity (38.9%), group 3 (control group) - 10 patients without liver steatosis with normal weight (11.1%).

Results: The prevalence of SIBO in 1 and 2 groups did not significantly differ (45.7% and 48.0%, respectively). Correlation analysis showed that the presence of SIBO positively correlated with the presence of symptoms of intestinal dyspepsia and number of defecation (r=0.33, r=0.30, respectively, p&LT; 0.05). It should be noted that children of the 1 group significantly differed from the 2 group by the higher levels of insulin and HOMA1-IR (p&LT; 0.05). The presence of SIBO showed positive correlation with insulin level (r=0.34; p&LT; 0.05) and insulin resistance markers (HOMA1-IR) (r=0.37; p&LT; 0.05). The presence of SIBO revealed a positive correlation with the ESR (r=0.3; p&LT; 0.05) and with APRI (r=0.66, p &LT; 0.05) in the general cohort of the subjects.

Conclusion: Changes of NAFLD patients intestinal microbiota have an effect on the clinical course, development of the systemic inflammatory response which is accompanied by the progression of structural changes in the liver and the insulin resistance.

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Objective and Study: To analyse the outcome of technical variant of liver transplantation (LT) (split, reduced, live-donor) and whole liver graft in paediatric LT recipients.

Methods: Retrospective analysis of all LT performed in a paediatric single transplant center between September 2008 and September 2017. LT were classified based on surgical techniques including whole graft, split graft (left lateral segment and extended-right lobe), reduced graft and live-donor graft. Recipient, donor and surgical characteristics were collected in a prospective database. The outcomes (morbidity and mortality) of all children were analysed. Exclusion criteria included LT combined with other organs, domino LT and re-transplantation.

Results: Out of 199, 180 LT were included [whole (n=36, 20%); split (n=87, 48.3%) including 83 (95.4%) left lateral segment and 4 (4.6%) extended right lobe; reduced (n=11, 6.1%); live-donor (n=46; 25.6%)]. Children receiving whole grafts were significantly older [116 (3-213) months] than these transplanted with other technical variant grafts [split: 16(3-198) months (p=0.0001); reduced: 4(0-22) months (p=0.0001); live-donor: 16(6-132) months (p=0.0001)] and waited on average 1.8 months longer on the waiting list [whole: 80(1-747) days; split: 63(1-536) days; reduced: 19(3-233) days]. Urgent status as indication for LT and Paediatric End-stage Liver Disease score ≥25 were more frequent in split and reduced graft recipients. One-month post-transplant morbidity was slightly higher for each type of technical variant compared to whole organ (16.7% whole, 36.8% split, 27.3% reduced, 39.1% live-donor). Liver grafts from younger donor were used as whole and reduced organs [whole: 8(0-58) years; split: 29(8-67) years; reduced: 33(22-59) years], while donor-recipient blood match was similar for all groups. Biliary complications were more common in technical variant (2.9% whole, 18.6% split, live-donor 17.4%, 0% reduced), while vascular complications were similar in all graft type (13.9% whole, 9.2% split, 9.1% reduced, 15.2% live-donor), of which portal vein thrombosis was the most frequent in all groups. Except for reduced graft (54.5% within 1 month of life and 36.4% received urgent transplantation), all other graft types had similar 4-year graft survival (100% live-donor, 97.2% whole, 93.1% split, 72.7% reduced) and patient survival (100% live-donor, 97.2% whole, 94.3% split, 72.7% reduced). One (4.8%) vascular complication (hepatic artery thrombosis) caused graft loss, while no biliary complication was responsible of graft failure. At the multivariate analysis graft type was not an independent predictor of graft loss.

Conclusion: Due to the limited availability of whole liver for paediatric transplantation, the majority of children receive technical variant grafts, which showed excellent outcomes in terms of graft and patient survival, while higher rate of 30-days post-transplant morbidity which however didn't impact on outcomes. Meticulous surgical technique as well as early diagnosis and treatment of technical complications are essential to ensure good results in technical variant LT, permitting to expand significantly the paediatric donor pool and to reduce time from listing to transplantation.

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Paediatric domino liver transplantation in maple syrup urine disease: Are multiple arteries a precluding factor?

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Objective and Study: To expand the paediatric donor pool, domino liver transplantation (DLT) using graft from children with maple syrup urine disease (MSUD) has been introduced to provide a whole liver from age-matched similarly size donor. As the priority is the safety of the first recipient, multiple hepatic arteries and insufficient vessels length in the domino graft might limit its use in the second recipient. The purpose of this single case report is to describe a feasible surgical technique for DLT in case of aberrant hepatic artery anatomy of the domino graft.

Method: We report a case on the use of a whole liver graft with hepatic artery anomalies obtained from a paediatric patient with MSUD and transplanted to a child with cirrhotic disease after complex vascular reconstruction.

Results: A 15 years-old male with MSUD underwent LT from a deceased donor and his liver was used as domino graft. Preoperative imaging showed a left hepatic artery rising from the common hepatic artery and a replaced right hepatic artery (RRHA) from the superior mesenteric artery. During the explant, the RRHA was retrieved up to the superior margin of the pancreas, while the stump of the gastroduodenal artery was included on the common hepatic artery to gain sufficient length for reconstruction. On bench, the RRHA was end-to-end anastomosed to the gastroduodenal artery stump (8/0Prolene). The domino graft was successfully transplanted to a 16 years-old male with biliary atresia and severe splenomegaly, in whom a single end-to-end hepatic artery anastomosis was performed (8/0Prolene). The post-operative course of the MSUD child was uneventful with normalization of serum leucine levels on unrestricted protein diet. The second recipient experienced on day 3 a splenic artery steal syndrome, resolved by splenic artery embolization.

Conclusion: DLT is feasible in children and should be considered for any MSUD case, even when arterial anomalies are present. Domino graft with multiple arteries can be safely used for paediatric recipients by surgical technique adjustment to gain sufficient length for vascular reconstruction.

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Assessment of encephalopathy with bispectral index in acute liver failure and relation to posttransplant neurological outcome

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Objectives and Study: Hepatic Encephalopathy is an important complication of acute liver failure (ALF). Lack of objective markers to assess degree of encephalopathy are still a big problem. Bispectral index (BIS) is a simple and non-invasive monitoring tool that determines the level of consciousness and is used in sedation monitoring. Aim of this study is determine the relationship between BIS index and grade of encephalopathy as well as laboratory parameters in children with ALF.

Method: Clinical and laboratory data of 20 patients who were diagnosed with ALF were recorded prospectively. Data were analysed by SPSS, using Spearman's correlation test, t test. A p-value < 0.05 was considered statistically significant.

Results: The pre-transplant PELD (pediatric end-stage liver disease) score was 42.4 ± 14.4; Duration of hepatic encephalopathy was 15.9 ± 1.3 hours; BIS index was 44.0 ± 10, serum ammonia level was 90 (84-238), lactate level was 4.5 (3-8) and blood pH level was 7.45 (7.39-7.50). Six patients had grade 3 to 4 HE, five patient had grade 3 HE, and nine patients had grade 1-2 HE. There was no correlation with the ammonia level in the admission, when there was a strong correlation (r = 0.82 p = 0.024) between the HE grade and the BIS index. Fourteen patients were underwent liver transplantation. Six patients were treated with supportive therapy. The duration of postoperative non-sedation wake-up was median 12 h (3-38), with strong correlation with pretransplant BIS index (r = 0.84, p = 0.01). In the early postoperative period, seizures were seen in two patient with preoperative stage 3-4 HE, but no abnormality other than slowing was detected in EEG.

Conclusion: The BIS index may be useful for assessment and follow up hepatic encephalopathy in children with ALF. Furthermore it may be used for decision of transplantation.

| Age yrs | 5 (0.8 -14) |
| PELD/MELD | 33 (14-52) |
| gender F/M | 8/12 |
| Weight (kg) | 11 (6-49) |
| Follow up time | 2.6 (6 hours -35 day) |
| Ammonia | 102(84-238) |
| Fibrinogen | 82 (42-112) |
| INR | 4.2 (3.2-8) |
| Lactic acid | 4.5 (3-8) |
| Blood pH | 7.45 (7.39-7.50) |

[Table 1. Demographic parameters]
**HEPATOLOGY - Transplantation**

**H-P-108**

**Different treatment strategies with different outcomes in a relative rare cohort: our experience in de novo autoimmune hepatitis**

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**Objectives and Study:** De novo autoimmune hepatitis (DNAIH) is a potentially life-threatening condition developing after liver transplantation. Data on treatment options and outcome in children are still sparse due to rarity of this condition. In a tertiary care centre, performing paediatric liver transplantation since 2000, we report our data on children with de novo autoimmune hepatitis.

**Method:** Retrospective chart review was conducted for children with liver transplantation, diagnosed during clinical follow-up with de novo autoimmune hepatitis in a single tertiary care centre between 2000 and 2017.

**Results:** Demographics, diagnosis before the liver transplant, type of donors (cadaveric-C, living related-LR), immunosuppressive drugs (ISTx, mycophenolate mofetil-MMF, azathioprine-AZA, cyclosporine-CYC, budesonide-B) at- and after the diagnosis of DNAIH and time to normalisation (t to N) of liver enzymes as well as current status of health are shown in Table-1. Among 168 children with liver transplant, 6 children (3.5%, 2 girls) developed DNAIH. Median time to DNAIH was 27.5 months (range: 2-90 months). Previous rejection history was evident in 2 children (33%). All children were treated with prednisolone (P) and tacrolimus (T) after the LTx unanimously. Median ALT and AST levels at the time of DNAIH diagnosis were 439.5 (range: 178-1614 IU/mL) and 242 (range: 88-1674 IU/mL) respectively. Positive serology of AIH was found in 3 children (2 LKM and 1 ANA): Patient 1: LKM-1 in 1/160 titre; patient 2: ANA 1/640 titre, patient 5: LKM-1 in 1/1280 titres. Mean IgG level was 1.88 g/dL (range: 1.24-2.20g/dL). Histopathological examination, histologic activity and fibrosis scoring were performed in all children by a single experienced paediatric liver pathologist. All children had liver biopsy findings consistent with DNAIH. In one child (Patient-6 in Table-1), working diagnosis was rejection, which changed after second biopsy and review of the previous biopsy. All other children had single episode of DNAIH, but one (Patient-1). In all children, DNAIH was initially managed with 2 mg/kg/day methylprednisolone together with either by reduction or discontinuation of calcineurin inhibitors; and azathioprine or mycophenolate mofetil was added. Median follow-up time after the DNAIH diagnosis was 11 months (range 6-202 months). Mean time to normalisation of liver enzymes for 7 episodes in 6 children was 6.8 months (1-15 months).

**Conclusion:** DNAIH in this cohort was managed with different treatment strategies defined for autoimmune hepatitis with a variety of different outcomes from end-stage liver disease to adverse effects. Most of the patients had quick resolution of the condition; however progression to cirrhosis might not be prevented in some patients in long term despite appropriate treatment. Further studies and long term follow-up will reveal the prognosis and factors contributing to outcome of DNAIH.
### Demographics of children with DNAIH

<table>
<thead>
<tr>
<th>Child/Patient</th>
<th>Current Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Type of donors (C/LR)</th>
<th>History of Rejection (Y=Yes N=No)</th>
<th>ISTx at DNAIH Diagnosis</th>
<th>ISTx after DNAIH Diagnosis</th>
<th>t to N (months)</th>
<th>Outcome-Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16 03/12</td>
<td>M</td>
<td>Acute liver failure of unknown aetiology</td>
<td>C</td>
<td>N</td>
<td>T</td>
<td>P,AZA</td>
<td>1.5</td>
<td>Healthy</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>M</td>
<td>Cirrhosis of unknown aetiology</td>
<td>LR</td>
<td>Y</td>
<td>T,MMF</td>
<td>P,MMF</td>
<td>3</td>
<td>Healthy</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>F</td>
<td>Mushroom poisoning-Acute liver failure</td>
<td>C</td>
<td>N</td>
<td>T</td>
<td>P,MMF</td>
<td>15</td>
<td>Healthy</td>
</tr>
<tr>
<td>5</td>
<td>10 03/12</td>
<td>F</td>
<td>Mushroom poisoning-Acute liver failure</td>
<td>LR</td>
<td>N</td>
<td>T</td>
<td>P,MMF</td>
<td>8</td>
<td>Healthy</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>M</td>
<td>Criggler-Najjar type-1</td>
<td>LR</td>
<td>Y</td>
<td>T,P,MMF</td>
<td>T,P,MMF</td>
<td>4.5</td>
<td>Severe cushingoid side effects Osteoporosis Renal stones due to hypercalciuria</td>
</tr>
</tbody>
</table>

Contact e-mail address: mscantez@yahoo.com
**Assessing the risk of transplantation in Alagille patients**

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²Guy's and St. Thomas’ Hospital/Evelina Children’s Hospital, London, United Kingdom

**Objectives and Study:** Liver transplantation (OLT) is required in up to 40% of Alagille syndrome (ALGS) patients. In the setting of cardiac involvement, with increased right sided heart pressures, the mortality has been historically high. In order to manage this risk, we have used a Dobutamine stress test (DST) to mimic the increased cardiac output required during reperfusion. We have previously recommended threshold criteria of increase of cardiac index of at least 40% with 20 μg/kg/min Dobutamine and/or right ventricular pressure < 50% of systemic pressure during DST.

The aim of the study was to review our management of cardiac lesions before OLT and the effect of these lesions on the short term outcome according to our evaluation and management.

**Method:** Retrospective data collection of 194 patients with ALGS from over 30 years period focussing on OLT and associated mortality. DST assessment was previously performed in the catheter laboratory, the recent protocol utilizes Interventional Hybrid Cardiac MRI Catheterization (XMR) for accurate simultaneous flow and cardiac output assessment. Patients with pre-transplant cardiac assessment (catheter DST or XMR DST) were recorded and comparison of the outcome post-transplant between no assessment, catheter DST and XMR DST eras was made.

**Results:** 89% patients (173/194) had a cardiac abnormality and 16% (31/194) had a heart intervention/correction. 44 patients (23%) were transplanted at a median age of 6.62 years (SD 6.85). 3 of 15 (20%) died early post-OLT in the pre-evaluation era for cardiac reasons. Pre-transplant cardiac assessment with catheter DST or XMR DST was performed in 33 cases. 15 had catheter DST before OLT - 9 were transplanted and all are alive. 19 patients had catheter XMR before OLT - 14 of them underwent OLT and all are alive; 3 were not listed for liver transplantation because of the severity of the cardiac pathology - 2 died subsequently from end stage liver disease and one is alive. Two had acceptable risk at XMR but were not listed due to stable liver disease.

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
<th>Pre Dob</th>
<th>Dob 10 μg</th>
<th>Dob 20 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheter DST summary</strong></td>
<td>HR (100 (SD 23))</td>
<td>110 (SD 26)</td>
<td>128 (SD 25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CI (4.4 (SD 1))</td>
<td>5.3 (SD 1.4)</td>
<td>6.4 (SD 1.5)</td>
<td></td>
</tr>
<tr>
<td><strong>XMR DST summary</strong></td>
<td>HR (85.7 (SD 19.5))</td>
<td>108.3 (SD 22.8)</td>
<td>132.1 (SD 25.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CI (3.5 (SD 1))</td>
<td>5.3 (SD 1.0)</td>
<td>5.5 (SD 0.9)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Patients with ALGS have high risk for complications in the transplant period. Assessing the cardiac status using DST has improved transplant outcomes, preventing early post-transplant deaths.

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Intrapatient variability in calcineurin inhibitor concentrations and liver graft fibrosis in paediatric liver transplant recipients

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Objectives and Study: Calcineurin inhibitors (CNIs), primary immunosuppressive agents for solid organ transplantation (SOT), play a crucial role in long-term graft and patient survival. High intrapatient variability (IPV) in CNIs exposure is recognized as a risk factor for rejection and poor long-term outcomes in SOT. This study aimed to assess the association of IPV in CNIs exposure and graft fibrosis in paediatric liver transplant recipients and to determine the risk factors of graft fibrosis.

Method: Children undergoing liver transplantation between January 2008 and January 2016 with a follow up period of 1-8 years were recruited. Subjects received either tacrolimus (Tac) or cyclosporine A (CsA). The IPV, expressed as coefficient of variation (CV) was calculated from CNIs whole-blood concentrations drawn between 6-12 months post transplantation. Liver fibrosis was detected by histology and transient elastography (TE). Clinical, biochemical, and ultrasonographic findings were recorded. Data was expressed as median (IQR).

Results: Nineteen children (52% male, 90% biliary atresia) were enrolled. Fifteen patients (79%) received Tac. Median age at the time of liver biopsy was 4 (2-6) years. The CV for Tac and CsA were 35.4% (24.5-47.3%) and 30.9% (23.7-50.4 %), respectively. Patients were divided into low (n=9) and high CV (n=10) groups using the median variability for each drug. All 3 patients who had biopsy-proven graft fibrosis were in high CV group. Only acute rejection within the first year post LT was associated with graft fibrosis ($P = 0.02$). For patients with any fibrosis ($\geq F1$), the AUROC for TE was 0.67 ($P = 0.2$). Using a cut-off value of 7.5 kPa, TE yielded 33% sensitivity and 100% specificity for predicting $\geq F1$ stage of fibrosis.

Conclusion: A high intrapatient variability in calcineurin inhibitor concentrations tends to be a risk factor of liver graft fibrosis. Liver biopsy in patients with high IPV may provide opportunities for the detection of graft fibrosis and prevention of further graft loss.

Acknowledgement: Financial support for this study was provided by the Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University and Thailand Research Fund (IRG5780015). We are particularly grateful for the assistance given by all the staff members of The Excellence Center of Organ Transplantation, King Chulalongkorn Memorial Hospital.

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Chronic liver disease presenting as acute liver failure

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Objectives and Study: There are no published studies focusing on the characteristics of children with chronic liver disease (CLD) whose presentation is with acute liver failure (ALF). In this study, we aimed to report the features and outcome of children with CLD presenting as ALF.

Methods: Retrospective study on children with ALF admitted to our centre between 1996 and 2017. Diagnosis of ALF was based on raised transaminases, INR ≥2.0 regardless of hepatic encephalopathy (HE), no known history of liver disease. According to EASL practice guidelines, children were considered as having a CLD presenting as ALF (ALF-CLD group) if the aetiology of ALF was: autoimmune hepatitis (AIH), Wilson disease (WD), Budd-Chiari syndrome (BCS), HBV reactivation, and metabolic disorders related due to enzyme deficiency. Baseline features of ALF-CLD patients were compared to those with a different aetiology of ALF (ALF-group). Predicting factors associated with a worse outcome (death or liver transplantation, LT) were analysed.

Results: 74 children [median age 4 years (IQR 1.0-8.8 yrs), M/F =36/38] were diagnosed with ALF; 18 patients, aged < 1 year, were excluded. Fifty-six patients [median age 6.6 years (IQR 2.7-11.7 yrs), M/F = 23/33] were divided into two groups: 22 patients in ALF-CLD group (AIH n=14, WD n=6, metabolic disorders n=2) and 34 in ALF-group (paracetamol overdose n=6, viral infections n=3, mushroom poisoning n=5, indeterminate-ALF n=20). In ALF-CLD patients, age at onset was higher [11.7 years (IQR 5.9-13.7 yrs) vs 6.6 (2.7-11.7), p < 0.01], the median values of ALT [790 UI/L (IQR 165-1200) vs 3878 UI/L (2442-6310), p< 0.001], albumin [3.1 g/dL (IQR 2.9-4.3) vs 3.5 g/dL (3.2-3.9), p< 0.001] and INR [3.4 (IQR 2.5-3.8) vs 4.4 (3.2-5.8), p=0.008] were lower, and the prevalence of splenomegaly (72.7% vs 5.9%, p < 0.001), ascites (31.8% vs 2.9%, p < 0.001) and cirrhosis on histology (45.5% vs 0%, p< 0.001) was higher compared to ALF-group. Prevalence of grade 3 or 4 HE was similar between the two groups (60 % in ALF-CLD vs 71% in ALF group, p>0.05). To determine the outcome and prognostic indicators we excluded 6 patients with paracetamol overdose who survived without requiring LT. Among 50 patients, 48 (96%) survived, 26 (54%) required LT and 22 (46%) recovered with medical therapy; 2 patients died on waiting list for LT. Transplant-free survival was higher in ALF-CLD group (64% vs 36% in ALF group, p=0.05) (figure 1). In all patients the median follow up time from the onset was 2 years (IQR 0.2-6.2 yrs), in transplanted children was 6.2 years (IQR 3-11 yrs). On multivariate analysis, the presence of an underlying CLD as aetiology of ALF halved the risk of LT or death (OR: 0.42; 95%CI: 0.18-0.98; P=0.045) while a prolonged INR ≥ 3.6 increased such risk by 3 folds (OR: 3.48; 95%CI: 1.42-8.53; P=0.006).

Conclusion: At our centre AIH and WD are the most common causes of CLD presenting as ALF. Laboratory and histological features at presentation are different between the two groups. ALF-CLD patients had a better outcome and transplant free survival. Our study suggests the need of a new definition and classification of ALF in children.
Transplant-free survival in 50 patients with ALF (ALF-CLD group vs ALF group)

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EBV serology pattern in pediatric liver transplant recipients

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Background: Epstein-Barr virus (EBV) infection can be associated with post-transplant lymphoproliferative disorder (PTLD). Thus, EBV serological tests are essential part of routine follow up of pediatric liver transplant recipients (PLTR). Serology might be distorted in chronic and immunosuppressed patients therefore the clinical implication of EBV serology remains unclear. Since their introduction, EBV viral load assays (PCR) provide an accurate monitoring tool for follow up in solid organ transplants.

Objective: Description of EBV serological patterns among PLTR patients with EBV infection proven by real-time viral load PCR.

Methods: Data of all PLTR patients diagnosed between 2004 and 2016 was reviewed for EBV serology and PCR viral load measurements. Changes in EBV serology were matched to the time of EBV viremia as proved by PCR.

Results: A significantly elevated EBV viral load detected by real-time PCR was found in 61 of 135 PLTR patients. In 24.5% of these patients IgG EBNA antibodies remained negative, although EBV infection or reinfection was proved by EBV viral load assay. In 15 patients, IgG EBNA antibodies changed from positive to negative during follow up. In 3% of EBV PCR positive PLTR patients, no VCA-IgG were ever detected. Only one PTLD case was found among patients with negative EBNA serology.

Conclusions: Our results show that some transplanted patients might not have any serological marker of EBV infection. Thus, EBV serology has very limited value in PLTR cases. Our findings support using EBV viral load assays as the diagnostic test of choice for EBV infections in PLTR patients.

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The role of ambulatory blood pressure monitoring after pediatric liver transplantation

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Objectives and Study: Due to immunosuppressive treatment, patients after liver transplantation (LTx) are at higher risk of arterial hypertension (HT), which is significant risk factor for cardiovascular disease. Ambulatory blood pressure (BP) monitoring (ABPM) is widely used as an extension of casual blood pressure (CBP) measurement. The aim of the study was to investigate the role of ABPM after pediatric LTx.

Method: CBP was defined as the mean of 2 manual measurements performed on day of ABPM and was classified as normal &LT; 90th percentile, pre-HT 90th-95th percentile, HT > 95th percentile. ABPM was monitored by an automated device according to current recommendations. The result was accepted if at least 70% of total measurement count was approved. Daytime and nighttime mean systolic BP (SBP) and diastolic BP (DBP) were compared to 95th percentile values for gender and height. Wake and sleep BP loads were calculated as the percent of readings at or above the 95th percentile. Nocturnal non-dipping (NND) was defined as &LT; 10% difference between the average daytime and nighttime BP. Classification of ABPM was based on current recommendations.

Results: The CBP, followed by 24h-ABPM were performed in 104 patients (63 females) at the mean age of 13.6 years (10.0-17.8), 10.5 years after LTx (5.1-16.8). Patients presented with stable graft function, and immunosuppression was based on tacrolimus (90%) or sirolimus (10%). Renal function by cystatine-c was >95th percentile in 8% (0.86±0.21). Mean BP was 82.2±6.0 (SBP 109.3±8.8; DBP 67.5±5.9). There were "white coat" HT in 0.9%, pre-HT in 1.9%, masked HT in 4.8%, and severe HT in 2.8% of patients. Two types of unclassified abnormalities were found. In 20% of patients there were normal CBP, mean ambulatory BP&LT; 95th percentile and BP loads > 25% and 27% had normal CBP, mean ambulatory BP&LT; 95th percentile and NND &LT; 10%.

Conclusion: Patients after LTx are at higher risk of arterial hypertension. ABPM should be performed routinely during follow-up as a supplement of CBP. Patients with borderline results or unclassified abnormalities should be closely monitored especially before transition to adult care. Significance of nocturnal non-dipping in children after LTx require further studies including assessment of organic cardiovascular damage.
**Objectives and Study:** Immunosuppression is a well-known risk factor for the development of *Clostridium difficile infection* (CDI). Patients after intestinal transplantation (ITx) are particularly at risk because of the high immunosuppression and the intestinal tropism of Clostridium difficile. However, few data are available on its severity after ITx and possible induction of rejection.

**Method:** We included retrospectively all patients after ITx with at least one year of graft survival. All samples positive for *Clostridium difficile* and its toxin were considered, whether the patient was symptomatic or not.

**Results:** Among the 57 ITx recipients (60 transplantations), 22 children (38%) developed culture-proven CDI, 12 of them after isolated small bowel Tx, 9 after liver-small bowel Tx, one after multivisceral Tx. The patients were a median of 8 year-old (4-18), and the time post-ITx was a median of 4 years (1-12). Twenty-two patients received steroids, 21 tacrolimus, 3 rapamycin, 4 azathioprine, 3 mycophenolate mofetil. Nine patients were hospitalized for a median time of 6.5 days (2-20), four with severe dehydration. Twenty patients had diarrhea, 8 with bloody stools, 4 with fever, one with hypothermia. Nine (40%) had received antibiotics for a median time of 19 days (7-60) before CDI. Two patients were asymptomatic. CDI was treated with metronidazole in 12 children, vancomycin in 5 and both of them in 3. Six out of 20 patients underwent an urgent endoscopy to rule out rejection. One child presented a severe rejection, treated with high dose steroids and thymoglobulins. One patient had together CDI and adenovirus, and a mild rejection on biopsies. He was treated by cidofovir and metronidazole and symptoms resolved. Recurrence of CDI was observed in 5 children, 3 of them treated with metronidazole and 2 with vancomycin. One of those had 3 CDI recurrences treated with vancomycin. At patients’ last follow-up, the stool number was the same as before CDI. Three patients had a positive *Clostridium* culture without symptoms.

**Conclusion:** CDI is more prevalent in children after ITx than after other solid organ Tx, and is most often symptomatic. CDI could trigger an intestinal rejection, and a low threshold for performing endoscopy should be the rule. Standard antibiotherapy is efficient to control the symptoms. However, recurrences are common, although we did not yet need to consider other treatments such as fidaxomicin or fecal transplantation.

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HEPATOLOGY - Transplantation

H-P-115

mTOR inhibitors in paediatric liver transplant recipients

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Objectives and Study: During the past decade, mTOR inhibitors (mTORi), everolimus and sirolimus, have been used more and more frequently after liver transplantation (LT). The aim of this study was to describe the use of mTORi in paediatric LT recipients.

Method: This cross-sectional study included 30 patients from 4 LT centres (three in France and one in Switzerland) who started receiving mTORi between May 2007 and March 2017.

Results: Twenty-one patients were male (70%) with a median age of 3.14 years (5 months-11.7 years) at LT and 9.31 years (1.2-17.1 years) at mOTRi introduction. Indications for mTORi introduction were pre-existing liver carcinoma in 11 (34%) patients, calcineurin inhibitor (CNI) nephrotoxicity in 9 (28%) patients, chronic rejection in 7 (22%) patients, de novo cancer after LT in 4 (13%) patients, or a combination in 3 patients. Everolimus was used in 28 patients. At last follow-up, mTORi was associated with CNI in 19 (63%) patients, 7 patient (23%) were under mTORi + mycophenolate mofetil treatment and 4 (13%) patients had a mTORi only immunosuppressive therapy. CNIs were withdrawn in 10 (30%) patients.

After a mean follow-up of 34 months (2-122), 50% of the patients presented at least one side-effect. Main side-effects included: hyperlipidemia (17%), proteinuria (13%), chronic cough, dermatitis and mucositis (10% each). Four patients presented two or more side-effects.

The mean estimated GFR (eGFR; Cockcroft-Gault) at baseline was 103±54 mL/min/1.73 m2 and 89±47 mL/min/1.73 m2 at the end of follow-up (p = 0.13). The same comparison for the 9 patients with CNI nephrotoxicity goes as following: 75±24 mL/min/1.73 m2 at baseline and 61±38 mL/min/1.73 m2 at the end of follow-up (p = 0.06).

The mean dose of mTORi was 1.1 mg/m2 (0.4-1-7) twice daily. The mean trough level of everolimus was 4.9 µg/l (0.9-10.5) at the end of follow-up.

Global everolimus discontinuation rate was 23% (10% [JD1] because of side-effects). Median duration of mTORi treatment before discontinuation was 11.5 months (4.4-106.9).

Biopsy-proven acute rejection occurred in 1 patient.

Conclusion: The results of our experience indicate that the use of mTORi is associated with adverse effects in 750% of patients leading to drug discontinuation in 1610%. No significance change in renal function had been found in this relatively long follow-up. Growing experience will improve the indications and the management of mTORi utilisation in in paediatric LT recipients.

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Do immunologic events in paediatric liver transplantation constitute a risk factor for amyloidosis?

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Objectives and Study: Hundred and sixty-eight paediatric liver transplants (LTx) have been performed in our institution since 2000. We conducted a study evaluating the risk of developing amyloidosis in children with LTx, after the death of a child transplanted for Tyrosinemia type 1 due to severe complications of amyloidosis, without any other risk factors. Sustained elevation of serum amyloid A (SAA) is a known risk factor for development of type AA amyloidosis. After LTx, the immunological interaction between the graft and the host may lead to a state of subclinical inflammation, which may increase the risk of amyloidosis.

Methods: Children who received a liver transplant at our centre and attended outpatient clinic regularly with complete follow-up data records were entered in the study prospectively. SAA levels were analysed by either cross-sectionally in all children (n=51), who had undergone LTx at least 6 months before study or prospectively at pre- and post-LT (1 week, 1 month and 6 months) in a subgroup of 7 children who received a liver transplant during the study. The results of transplanted children were compared with SAA levels of children with acute infection symptoms without underlying chronic conditions, seen in outpatient clinic (acute infection group, n=50) and SAA levels of children with an established diagnosis of Familial Mediterranean Fever in remission (FMF group, n= 49). The correlation of SAA levels with previous rejection episodes, recurrent infections and other possible inflammatory events were analysed. Ethics approval was obtained from the local board of ethics.

Results: In the study group with 51 transplanted children (25 girls, 26 boys median age: 10.6 years, range: 1.1-20.5) median follow-up after LTx was 61.90 months (range: 6.27-190.40). Rejection history was positive in 7 out of 51. Median SAA was 4.15 mg/L (range: 0.69-71.80 mg/L). SAA was > 10 mg/L in 9 children (17.6%, range 10.2-71.8 mg/L). In acute infection group (50 children, 21 girls; mean age 6.49±4.30, range: 0.5-17.2) median SAA was 172 mg/L (range: 1.50-961mg/L). In 48 children (98%) with acute infection SAA was >10 mg/dL (range: 21.9- 961 mg/L). SAA was significantly higher in the acute infection group (p&LT; 0.01). Median SAA levels of FMF patients (21 girls, median age: 12.6 years, range: 4-19.7) was 3.6 mg/L (range: 0.1-49.4mg/L). In 6 children (12.2%) with FMF, SAA was >10 mg/dL (range: 10.2-49.4 mg/L). SAA levels were not significantly different between cross-sectional LTx and FMF group. In the prospective LTx group with 7 children (5 girls) median SAA prior to LTx was 3.5 mg/L (range: 0.77 - 4.96 mg/L). One week, one month and six months after the LTx, median SAA levels were 35.4 (range: 15.2-198), 34.0 (range: 3-190), and 3.4 (range: 0.69-71.8) mg/L respectively. SAA levels at one week and one month after the LTx were statistically higher compared to levels of 6 months post-LT (p&LT; 0.05).

Conclusion: After LTx, the graft and the host reach a state of immunologic equilibrium with time. As the intensity of the interaction between the graft and the host decreases, production of SAA decreases by posttransplant sixth month. The elevated SAA levels in the early posttransplant period do not seem to be high enough or persist long enough to increase the risk for the development of amyloidosis.

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Early Chylous ascites in paediatric liver transplantation: incidence, risk factors and outcome

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Objectives and Study: Chylous ascites (CA) after liver transplantation (LT) is scarcely studied in children. In this large single centre study, we aimed to evaluate the incidence, risk factors and outcome of CA in paediatric recipients of LT.

Method: Data from 337 consecutive isolated LT performed between 2000 and 2016 were reviewed. CA was diagnosed based on the presence of "milky" or creamy colour of peritoneal fluid and positive chylomicron detection or triglycerides ≥187 mg/dL in peritoneal fluid within 60 days after LT. Recipients were excluded for pre-operative diagnosis of CA and death or re-transplantation within 30 days post-LT. Data were analysed using Student t-test, Mann-Whitney U test and the chi-square test when appropriate. Logistic regression univariate analysis was employed for risk analysis.

Results: The study cohort comprised 317 LT (153 living donor and 164 deceased donor) in 310 recipients with a median age at LT of 2.71 (range 0.08-17.93) years. CA developed after LT in 18/317 LT (5.7%) at a median of 12 (range 7-23) days post LT. Pre-LT ascites (OR 7.28, 95% CI 2.33-22.72), portal hypertension (OR 8.31, 95% CI 1.88-36.82) and weight ≤ 10 Kg (OR 6.5, 95% CI 2.1-20.44) were associated with the development of CA. Improved nutritional status at LT, as reflected by weight z-score and height z-score, was associated with a lower likelihood for CA development (OR 0.71, 95% CI 0.51-0.98 and OR 0.96, 95% CI 0.94-0.99, respectively). Abdominal surgery prior to LT, underlying diagnosis, graft type, use of arterial conduit graft and presence of a post-operative surgical peritoneal drain were not associated with a higher CA risk. Initial treatment of CA in all patients included peritoneal fluid drainage through peritoneal drain and dietary modifications. Initial dietary modifications included high medium chain triglyceride (MCT) diet (n=10) or nil per os + parenteral nutrition followed by high MCT diet (n=8). Patients received high MCT diet for a median of 50.3 (range 2-121) days. Peritoneal drains were removed within a median of 18 (range 3-45) days after CA diagnosis. Octreotide was used in two cases. CA diagnosis was associated with an increase in hospital length of stay (CA 37.5 days vs. non-CA 24 days; p=0.001) but not with reduced patient or graft survival.

Conclusion: CA is uncommon after paediatric LT and doesn't impact long-term graft and patient outcome. The presence of pre-operative ascites and portal hypertension, poor nutritional status and weight ≤10 Kg are risk factors for the development of CA. Dietary modifications and CA drainage with peritoneal drains led to resolution of CA in the majority of patients.

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Lessons learned from 250 pediatric living donor liver transplantsations in a single center

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Objectives and Study: The experience of pediatric living donor transplantation (LDLT) has been accumulating since its first performance in 1989. We aimed to learn the characteristics and outcome of pediatric LDLT for 20 years in Asan medical center located in Korea.

Method: This retrospective review between 1994 and 2016 included 250 pediatric cases with LDLT performed at a single center. Recipients whose first liver transplant (LT) was deceased donor were excluded. Outcome was analyzed by comparing the patient and graft survival in two groups, 1994-2005 and 2006-2016.

Results: Two hundred fifty LDLT were performed in 241 children. Thirty patients (5.4%) required a first re-transplantation, 3 patients (1.2%) required a second re-transplantation. ABO incompatible LDLT were performed in 13 cases (5.4%). Median age at liver transplantation was 1.7 years (range 0.25-17). Median body weight at liver transplantation was 11kg (range 4.9-80). Graft-recipient weight ratios were 4.1% (2.5-5.8), 3.0% (1.5-4.5), 1.8% (1.0-3.3), 1.4% (0.9-1.6), and 0.9% (0.7-1.7) in weight 6 or less, 7-10, 11-20, 21-30, and 31kg and more, respectively. The top 3 causes of LT were biliary atresia (118/241, 49%), acute liver failure (54/241, 22.4%), and Wilson disease (17/241, 7.1%). Two hundred fifty two grafts including 2 dual donors were used in this study. The median age of donors was 33 years (16-55). The fatty change of graft was the most frequent in 0-10% (180/210, 85.8%). From 1994 to 2005, cumulative patient/graft survival rates at 1-, 5-, and 10-year were 89.8/88.2, 83.3/81.8, and 82.4/80.0%, respectively. Patient survival rates at 1-, 5-, and 10-year survival rates after 2006 were significantly increased 94.8/92.9, 94.8/91.1, and 93.5/91.1%, respectively.

Conclusion: The outcome of pediatric LDLT in this series has been improved over time, as the short-term success in survival reflected the long-term outcome.

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**Objectives and Study:** Graft versus host disease (GvHD) is a major complication after haematopoietic stem-cell transplantation and much less common after solid organ transplant and rare after liver transplantation. Early symptoms can resemble viral infections or drug-reactions and thus it may be under-investigated. There are no standard treatment guidelines for GvHD after paediatric liver transplantation. The purpose of this study was to review all reported cases of GvHD reported in paediatric liver transplantation to date.

**Method:** Literature review of all English-language full-text articles published between 1990 and 2017. Case series articles and case reports were reviewed and collated. Symptoms, diagnostic investigations, treatments and outcomes were described for all reported cases.

**Results:** 13 patients were identified with GvHD after liver transplantation (LLS OLT or LDLT). Acute GvHD (aGvHD) was reported in 9 patients (earliest: day 11, latest: day 95), chronic (cGvHD) in 1 (day 1825) and late-onset GvHD in 3 (day 140, 160 and 480). Skin manifestations occurred in 11/13 of patients (84.6%). Gastrointestinal symptoms were reported in 9/13 (69.2%); out of which diarrhoea in 8/9 (88.8%), vomiting in 3/9 (33.3%) and PR bleeding in 2/9 (22.2%). Fever was present in 8/13 (61.5%). Haematological/bone marrow symptoms were reported in 10/13 (76.9%); pancytopenia in 8/10 (80%) and haemolytic anaemia (HA) in 3/10 (30%). Skin biopsy was positive for GvHD in 5/13 (38.5%), gastrointestinal biopsy showed GvHD in 4/13 (30.8%) and donor HLA markers for chimerism were positive in 8/13 (61.5%). The most common treatment was steroids (MEP or PSL), used in 8/13 (61.5%). Discontinuation of immunosuppression was trialed in 4/13 (30.8%); 2 continued to have uncontrolled GvHD, whereas in the other 2, the GvHD resolved. Polyclonal anti-thymocyte globulin (ATG) was used in combination with other immunosuppression in 3 patients. In the reviewed literature, 7/13 (53.8%) of the cases were reported as having complete resolution of GvHD, whereas 6/13 (46.2%) had uncontrolled GvHD (multiorgan involvement, cGvHD or death).

**Conclusion:** GvHD in paediatric liver transplantation is difficult to treat and has a high mortality rate. Prompt consideration of symptoms is desirable to initiate treatment early. A maculopapular skin rash, especially accompanied by fever or GI symptoms, should always be considered as a sign of GvHD, and should prompt early investigation and modification of the treatment. Biopsies from all the tissues involved can help to differentiate between GvHD staging and monitoring. Better recognition of symptoms and understanding of novel therapies available offer hope for the future.
Hepatitis related aplastic anemia incidence in pediatric liver transplantations after seronegative fulminant hepatitis

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Objectives and Study: Hepatitis related aplastic anemia (HIAA) is a chart of bone marrow failure after acute hepatitis. It can develop in 0.03-0.2% after acute hepatitis. Hepatitis viruses A, B, C, D, E and G as well as parvovirus, TTV and non A-E hepatitis viruses cause HIAA. However, most HIAA etiology has seronegative viral hepatitis. Determination of the incidence of aplastic anemia in patients with liver transplantation due to non-A, non-B, non-C fulminant hepatitis in Ege University Children’s Hospital and Kent Hospital between 1998 and 2017 and the treatment response, clinical characteristics and prognosis of patients with hepatitis related aplastic anemia were targeted.

Method: This retrospective study included patients with non-A, non-B, non-C fulminant hepatitis tablets in the Ege University Children’s Hospital and Special City Hospital between the dates of 1998-2017 and the ones developing hepatic aplastic anemia. Non-A, non-B, non-C fulminant hepatitis diagnosed with metabolic disease, autoimmune hepatitis, toxin exposure and hepatitis A-B-C virus infection were excluded. Patients had to have at least 2 hepatic encephalopathy and deterioration of liver synthesis function. For the diagnosis of aplastic anemia, all patients with at least 2 of the criteria of peripheral kinetics of neutrophil count of 200-500 / mm3, platelet < 20bin / mm3, reticulocyte < 40bin / mm3 were aspirated and bone marrow was diagnosed as having 30%. Intermittent hemogram, biochemistry, immunosuppressive drug blood level and bleeding parameters were taken from the patients during the follow-up.

Results: The etiology of 18 (40.9%) of 44 patients with liver transplantation who were diagnosed with fulminant hepatitis was non-A, non-B and non-C hepatitis. Four of these 12 patients (33.3%) developed aplastic anemia. Two of the patients are girls. The average age is 6.5 years (2-10 years). Bone marrow transplantation was performed to 1 patient (25.0%). 2 patients received immunosuppressive treatment (granulocyte colony stimulating factor, antithymocyte globulin rabbit,Cyclosporine,Prednisolon. One patient died despite intensive support treatment.

Conclusion: Hepatitis related aplastic anemia can develop after seronegative viral hepatitis, which can be fatal if left untreated. It can even be seen in the period when the acute hepatitis tabulation is correct. For this reason, it should always be kept in mind when developing cytopenias during and after viral hepatitis.
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<td>G-CSF rATG CYCLOSPORINE PREDNISOLON</td>
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[The general characteristics of the patients]

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Absence of oesophageal varices in children with splenomegaly and advanced intestinal failure associated liver disease

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Objectives and Study: Children with splenomegaly and portal hypertension due to primary liver disease demonstrate gastro-oesophageal varices (GOV) on oesophago-gastroduodenoscopy (OGD). Intestinal failure-associated liver disease (IFALD) is a secondary liver disease caused by continuous use of parenteral nutrition (PN). IFALD leads to hepatobiliary dysfunction which may progress to biliary cirrhosis, portal hypertension and end stage liver disease. Children on PN for intestinal failure who develop end stage liver disease have a 100% mortality rate after 5 years without combined liver and small bowel transplantation (SBTx). The aim was to evaluate the current methods for identification of liver disease in children with IFALD referred for SBTx assessment.

Method: Retrospective chart review of children with IFALD, who underwent assessment for SBTx (Sept. 2004 - Dec. 2016) at Birmingham Children's Hospital. Children who had both OGD and liver biopsy performed were included. IFALD was defined as ≥ one episode of a total Bilirubin persistent over 100 mmol/L not caused by a line infection for >4 weeks, combined with features of portal hypertension. Basic investigations included: liver function tests, abdominal ultrasound, OGD, and liver biopsy. Spleen size, liver biopsy and presence of GOV were recorded.

Results: 49 children, 29 (59%) males, were included. Median age at time of SBTx assessment was 2.5 years (range 0.4-15.9 years) with a background of: 24 (49%) short bowel syndrome; 19 (39%) dysmaturity disorders; and 6 (12%) primary mucosal disorder. Abdominal ultrasound showed: 40/48 (83%) splenomegaly; 26/49 (53%) hepatomegaly; 2/49 (4%) ascites. In 1 patient the spleen was not measurable due to splenectomy. OGD revealed varices in 8 children (16%) of which 7 had grade I varices and 1 child had grade III varices. However, 33 children (67%) with splenomegaly had no varices on OGD while no children with a normal size spleen had GOV on OGD. There was no difference in prevalence of varices in patients with short bowel syndrome 4/24 (17%) and full length bowel 4/25 (16%). Liver biopsy showed: 4 children (8%) with no fibrosis; 22 children (45%) with mild fibrosis, and 23 children (47%) with moderate/severe fibrosis. Moreover, 3 children with mild fibrosis and 2 children with moderate/severe fibrosis had a normal size spleen. Likewise, 17 children with mild fibrosis and 20 children with moderate/severe fibrosis had no GOV on OGD. There was no difference in prevalence of varices in patients with mild fibrosis on liver biopsy compared to patients showing severe fibrosis (5 [19%] vs 3 [13%]; p=0.7). We found a significant association between degree of fibrosis and bilirubin level (95% CI 0.002-0.009, p=0.007) but no association between degree of fibrosis and platelets (95% CI -0.003-0.004, p=0.8) or prothrombine time (95% CI -0.9-0.17, p=0.2).

Conclusion: In children with IFALD, splenomegaly is common and GOV are infrequent. The degree of liver fibrosis does not correlate with presence of GOV. Therefore, conventional methods for determining portal hypertension (splenomegaly, gastrooesophageal varices) are not useful in assessing the severity of IFALD. Alternative tests/methods such as hepatic venous pressure gradient and transient electrography needs to be validated to help determine the severity of IFALD.

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**Objectives and Study:** Burkitt lymphoma (BL) is a post-transplant lymphoproliferative disorder (PTLD) different from other monomorphic PTLDs (M-PTLDs). We report clinical presentation and pathologic findings in 6 pediatric cases.

**Method:** We included patients that undergone a liver transplantation (LT) at Sainte Justine Hospital (Montreal) or in The Children hospital of Lyon, from 1991 to 2017, (aged ≤18 years). During this period, 10 patients presented monomorphic PTLDs (M-PTLDs), 6 of which were Burkitt lymphoma (BL).

**Results:** The median age at transplantation, for the 6 children (5 boys, 1 girls) with BL, was 21.5 months (range 6 - 159 months), and biliary atresia was the main indication (3/6). BL had an abdominal presentation in majority of cases (5/6). Patients displayed a monomorphic population of small to intermediate-sized, non-cleaved, lymphoid elements with a “starry-sky” pattern. The immunophenotype in patients available for analysis was CD20+ (n =6/6), CD10+ (n = 6/6), Bcl-6+ (n = 6/6), Ki-67/MIB-1 proliferation index (n = 5/5), and negative for TdT (n = 5/5). Pre-transplant Epstein-Barr virus serology was negative in 4 patients (n = 4/6). At the time of BL diagnosis, all patients showed high EBV viral loads estimated by quantitative PCR testing between 16000 and 20^6 copies/ml. The PCR was positive since a median time of 26.5 months (range, 1-40 months).

The median time from transplantation to diagnosis was 33 months (range, 3-46 months). All patients were currently alive after chemotherapy, with median disease-free time of 14.5 years from diagnosis (range, 2-19 years).

**Conclusion:** Post-transplant-BL is strongly associated with high EBV viral loads and represented a distinct monomorphic PTLD. Managed aggressively with decreased immunosuppression and specific chemotherapy must lead to a favorable outcome. These data also lead to discuss the modality of monitoring and the establishment of early treatment, with anti CD 20, for transplanted patients who retain high EBV viral loads.

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Objectives and Study: Paediatric acute liver failure (ALF) differs from adult ALF. Because paediatric ALF has various aetiologies, and little is known about natural courses of ALF, determining the outcome of paediatric ALF is challenging. The aim of this study was to identify predictors of outcomes of paediatric ALF.

Method: This study reviewed data for 62 paediatric ALF from 2004 to 2017 at the Department of Paediatrics in the Seoul National University Children's Hospital. Laboratory data during the first seven days after diagnosis were collected: peak total bilirubin (TB), TB at diagnosis, peak prothrombin time International Normalized Ratio (INR), INR at diagnosis, peak ammonia, the difference between the peak TB and TB at diagnosis (i.e., delta TB), the difference between the peak PT INR and PT INR at diagnosis (i.e., delta INR). Patients were categorized into spontaneous recovery (group 1) and death or liver transplantation (group 2).

Results: Sixty-two children (15 children in group 1, 47 children in group 2) were enrolled. The aetiologies were: indeterminate (45.2%), Wilson's disease (11.3%), drug-induced (9.7%), viral infection (8.1%), hematologic malignancy (16.2%), neonatal hemochromatosis (4.8%), neonatal intrahepatic cholestasis caused by citrin deficiency (3.2%) and biliary atresia (1.6%). Univariate analysis revealed that delta TB, delta INR, and peak ammonia were significantly different between the groups (p<0.05 for all). The results of receiver operating characteristic curves (ROC) indicated that optimal cut-off values to discriminate between group 1 and group 2 were; delta TB > 4.85 mg/dL, delta INR > 0.25 and peak ammonia > 172 µmol/L. The logistic regression model for these three cut-off values generated the area under the ROC (AUC) of 0.881 (95% confidence interval: 0.793-0.969). We conducted the logistic regression model for the above three cut-off values in patient with spontaneous recovery (n=15) and patient with death (n=22), and this logistic regression model yielded an AUC of 0.939 (95% confidence interval: 0.865-1.000).

Conclusion: In paediatric ALF, the difference between the peak TB and TB at diagnosis and the difference between the peak INR and INR at diagnosis might be better prognostic values than peak TB and peak INR.

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**Resistance index of hepatic artery can predict anastomotic biliary complications after liver transplantation in pediatric patients**

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**Objectives and Study:** Biliary complications remain an important cause of morbidity after pediatric liver transplantation. Inadequate arterial supply to the bile duct after transplantation plays an important role for developing anastomotic biliary complications. We aimed to elucidate the relationship between the resistance index (RI) of hepatic artery and the anastomotic biliary complications after liver transplantation in pediatric patients.

**Method:** This is a retrospective, case-control study. We enrolled 11 pediatric patients under 18 years of age with anastomotic biliary complication after liver transplantation and 26 pediatric transplanted patients without biliary complication as control group. Baseline characteristics were obtained, and all patients received liver doppler ultrasonography from 2 months to 12 months after liver transplantation. The RI of hepatic artery was measured by: \( \text{RI} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}} \).

**Results:** We used the receiver operating characteristic (ROC) curve analysis in these 37 pediatric patients and found a cutoff point of \( \text{RI} \leq 0.57 \) (63.6% sensitivity and 92.3% specificity) for the best prediction of anastomotic biliary complications. \( \text{RI} \leq 0.57 \) is significant difference between two groups (Odds ratio=21, 95% CI=3.16-139.66, \( \text{P}=0.002 \)). The cox proportional hazard analysis also showed the significance of \( \text{RI} \leq 0.57 \) in the prediction of biliary complications (Hazard ratio=8.11, 95% CI=2.35-28.01, \( \text{P}=0.001 \)) after liver transplantation.

**Conclusion:** The RI of hepatic artery \( \leq 0.57 \) may serve as an important non-invasive clinical predictor for anastomotic biliary complications after liver transplantation in children.
HEPATOLOGY - Transplantation

H-P-125

How small is small increasing the risk of complications in pediatric liver transplants? Experience from a high volume living related pediatric liver transplant centre

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Objectives and Study: The purpose of this study was to determine effect of weight and pre-transplant nutritional status on post-transplant outcomes (complications, length of hospital stay, sepsis and survival).

Methods: We conducted a retrospective review of all children who received a living related liver transplant (LDLT) between September 2004 and November 2017. Children were divided into 4 groups on the basis of weight (A- &LT; 6.5kg; B- 6.6 to 10kg; C- 10.1 to 15kgs and D- >15kgs). Each group was further divided on the basis of pre op z score (weight for age) into normal and malnourished (< 2SD). Outcomes between these groups were compared in terms of mean hospital and ICU stay, vascular, biliary complications, sepsis and survival.

Results: Data was analyzed for a total of 238 children. Mean age in months- 7.34; 14.1; 33.2 and 115.4 respectively in Group A, B C and D. Group A (&LT; 6.5kgs) had significantly more surgical complications and ICU stay as compared to rest 3 groups (p&LT; 0.05). Further in group A and D the malnourished kids had significantly higher surgical complications (p&LT; 0.05). The complications were no different between group B vs C/D. Group A and B had significantly high rate of sepsis as compared to rest 2 groups. Though group A had high rate of sepsis than group B but it was not statistically significant. One year survival rate, not statistically different in Group A, B, D was 88.5,88 and 94% respectively. Group C had the 100% 1 year survival. In all four groups the survival was not affected by normal weight Vs weight < 2SD pre transplant (p >0.05).

Conclusions: The surgical complications, sepsis and ICU stay was highest in &LT; 6.5 Kg though no statistical difference in survival. Weight &LT; 2SD further increased complications. Complications were comparable between > 6.5 Kg and > 10 Kg.

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Successful experience of liver transplantation in Maple Syrup Urine Disease (MSUD): a single center experience

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Objectives and Study: MSUD is an autosomal recessive metabolic disorder characterized by impaired activity of the branched-chain acid dehydrogenase complex. If left untreated, MSUD can result in mental illness and even death. Liver transplantation (LT) has been effective in patients with MSUD. Liver from patients with MSUD can be used for domino LT (DLT).

Methods and Results: Between 2008 and 2017, 5 out of 192 (2.7%) children underwent LT for MSUD, with mean age of 47.5 months. Indications to LT were poor metabolic control, expressed as psychomotor disabilities and poor quality of life. Before and after LT, all children completed IQ and adaptive testing to assess the development and underwent brain RM. A patient with MSUD who underwent LT provided a whole liver (WL) for DLT in a child with biliary cirrhosis. 4 patients received cadaveric grafts (2 left lateral segment [LLS], 1 WL) and 1 a LLS from living related liver transplant (LRLT) from the heterozygous father. Patient and graft survival were 100% and all children had normal graft function after a median follow up of 6 months (range 5-23). The median length of hospital stay after LT was 25.5 days (range 20-35 days). No surgical complication was seen after LT. One patient showed acute liver rejection within 30 days, requiring steroids pulse. After LT, all patients had noticeable decrease branched-chain amino-acids and alloisoleucine, despite the increase of the proteins in the diet to the normal requirements for age. No post-LT metabolic decompensation was documented, including LDLR and DLT recipients. All the children had normal graft function after a median follow up of 6 months (range 5.25-22.5). All children had neurological improvement or stability. DLT recipient maintained normal levels of amino acids, with no detectable alloisoleucine on free diet. One-year post LT, a patient presented with intestinal distension and elevated pancreatic enzymes, without hyperammonemia or metabolic decompensation and recovered after exploratory laparotomy.

Conclusion: In our experience, LT in MSUD improves quality of life, reducing the risk of metabolic decompensation with a protein-unrestricted diet, even when LRLT from heterozygous donor is performed. Liver from MSUD patients can be used safely in pediatric DLT to increase the graft pool.

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Autoimmune haemolytic anaemia with giant cell hepatitis and concurrent bile salt export pump deficiency: challenges in diagnosis and management

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Objectives and Study: Autoimmune haemolytic anaemia with Giant Cell Hepatitis (AIH-GCH) is a rare, progressive disease affecting infants and young children. The disease is characterised by Coombs-positive haemolytic anaemia and severe hepatic dysfunction with giant cell transformation. Prognosis is fatal despite aggressive immunosuppression, with risk of recurrence following liver transplantation.1,2 The mechanism of hepatic injury is not completely understood. Several authors have published work supporting complement mediated hepatocyte injury by demonstrating positive complement staining with C5b9 on liver biopsies.3 Increasing evidence supports use of Rituximab, an anti-CD-20 monoclonal antibody as treatment for AIH-GCH.4 We present a case of a male infant with AIH-GCH treated with Rituximab followed by liver transplant once genetic studies confirmed BSEP deficiency.

Method: Clinical, laboratory and histology findings together with treatment outcomes were reported.

Results: A male infant presented in Brescia (Italy) at eight weeks of age with conjugated hyperbilirubinaemia, transaminitis and Coombs-positive haemolytic anaemia. He received three blood transfusions and one dose of intravenous Immunoglobulin G. He received two further blood transfusions at his local hospital upon relocating to the United Kingdom. He was referred to our centre at 15 weeks of age with hepatosplenomegaly, jaundice, transaminitis, anaemia and resistant coagulopathy (bilirubin 376umol/L, ALT 485u/L, haemoglobin 75g/L and INR 1.7). He underwent complete liver failure workup. Ongoing haemolysis was evidenced by blood film examination, Coomb’s positivity and low serum haptoglobulins with repeated blood transfusion requirement every 7-9 days. Liver biopsy demonstrated cholestatic giant cell hepatitis, hence diagnosis of AIH-GCH made. This was further supported by positive C5b9 immunostaining on liver histology.

He was initially managed with intravenous Methylprednisolone (2mg/kg/dose). Beneficial effect was observed for only 48 hours. This was followed by three-day course at a higher dose (10mg/kg/dose) and subsequent weaning regime. Mycophenolate Mofetil was added to treatment (20mg/kg/dose) and he received four courses of Rituximab with last dose given at 21 weeks of age. Blood counts demonstrated satisfactory B-cell depletion however no improvement to liver function with resultant development of Grade 1 encephalopathy. Genetic testing returned at 24 weeks of age detected homozygous mutation in ABCB11 confirming additional diagnosis of BSEP deficiency (Table 1).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Nucleotide</th>
<th>Status</th>
<th>Protein Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB11</td>
<td>c.2426C&gt;T</td>
<td>Homozygous</td>
<td>p.(Ser809Phe)</td>
</tr>
</tbody>
</table>

[Table 1: Result of genetic panel]

He received a cadaveric graft (split) at 29 weeks of age. His latest transfusion requirement was three days prior to transplant. Post transplantation, he suffered an episode of acute cellular rejection (day 8) treated with corticosteroids. He was also treated for an episode of bacteraemia with Serratia marcescens (day 21). Liver biopsy six weeks post-transplant showed no evidence of recurrence of GCH. He remains surviving at one year and five months of age.

Conclusion: To our knowledge, this is the first reported case of AIH-GCH with concurrent BSEP deficiency successfully treated with Rituximab and liver transplantation. However, given the rarity of its presentation, it is difficult to ascertain treatment and long term prognosis for this condition.

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Single center long term follow up of Kasai portoenterostomy for Biliary Atresia patients

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Background: Biliary atresia (BA) is a progressive inflammatory destructive disease. BA is the leading cause of cholestasis in the newborn period, and the single most frequent indication for Orthotopic Liver Transplantation (OLT) in children. Kasai portoenterostomy (KPE) may halt the progression of liver disease but in most patients is only a bridge to liver transplantation.

Objective: Describe the long term follow up of pediatric BA patients who underwent KPE at a tertiary pediatric liver transplant center.

Methods: Data was collected from the records of all BA patients followed at our center between 1994 and October 2017. Data included medical charts, operation reports, and follow-up visits and laboratory data. Patients were considered as successful KPE if they survived with their native liver beyond 2 years of age and were considered as failed KPE if they required OLT before 2 years of age.

Results: Data was retrieved for all BA patients (n=90). As 3 infants underwent OLT without having KPE, we evaluated 87 patients who underwent KPE at an average age of 7.76 weeks of age (3-16 weeks range). Successful KPE was achieved in 42/87 (48.2%). The successful KPE group had an average native liver length of life of 5.3 years (range of 2-13 years). Overall, A total of 47/90 patients underwent OLT during follow up years. Six patients out of the whole BA group (6.6%) have died over the years (3 due to OLT complications, 2 on the waiting list for OLT, 1 after KPE due to complicated cardiac disease).

Conclusions: As reported in other large cohorts, KPE may prevent the need for OLT and should be attempted in all cases of BA.
What is the long-term outlook for young people following liver transplant? A retrospective analysis of physical and psychosocial adaptation

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Background: Liver transplantation (LT) is a successful treatment for end-stage liver disease. There are little data on the long-term outcome of patients who underwent LT in childhood.

Aim: To assess the long-term impact of transplantation and immunosuppression in young people who survived LT for more than 15 years.

Subjects/Methods: All patients who survived for more than 15 years post LT were included. Data included growth parameters (height/weight/BMI), liver/renal function, evidence of hypertension, hyperlipidemia, graft function, psychological disorders, education/employment status and socially accepted behaviours.

Results: 143 patients who underwent LT (1985-2000) aged a median of 25 months (range 15 days-16 years) were alive and >15 years post-transplant at last follow-up. The median post-transplant survival was 18.96 years, range 15 years to 27.04 years. 62% of survivors had normally functioning grafts. The main causes of graft dysfunction in survivors were chronic hepatitis/fibrosis in 11%. Long-term complications included renal dysfunction (16.7% had a calculated GFR < 70ml/min/1.73m² and 9 patients required a renal transplant). 27% required oral antihypertensive therapy. 9% had had post-transplant lymphoproliferative disorders/lymphoma/leukaemia. 61% of this cohort was compliant with both medication and outpatient attendance. 33% admitted to being non-compliant with medication and 19% intentionally missed clinic appointments. Young people in this cohort were considered healthier than the average UK teenager with regards to BMI, smoking and alcohol drinking behaviours. 95% of patients had completed higher education prior to employment or remained in higher education.

Conclusion: The long-term outcome of LT in childhood is good, with most patients having little or no graft dysfunction and minimal side effects of immunosuppression. Survivors contribute well to society and overall are healthier than the general population with only 38% drinking alcohol and 18% smoking regularly and only 7% having a BMI consistent with obesity.

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A retrospective review of patients presenting to a tertiary liver centre with primary liver and cardiac disease

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Background: Children with liver unit disease may have cardiac disease as part of their disease spectrum. This may be primary or secondary. Primary causes include inherited liver disease, metabolic disorder or idiopathic. Co-existent cardiac disease may lead to extra challenges with regard to management, or be a contra-indication for transplantation.

Aims/Objectives: 1. Identify total number of patients presenting with liver and cardiac disease 2. Evaluate management and outcome including selection for liver transplantation

Patients/Methods: A retrospective study evaluating case notes of patients presenting to tertiary hepatology services from 1987-2017. Inclusion criteria: All patients of BCH Liver Unit with a diagnosis of primary liver and cardiac disease.

Results: 535 patients had a primary hepatic and cardiac diagnosis. 130 (24%) were assessed for liver transplantation, 81 patients (62% of the assessed cohort) underwent liver transplantation. 2 patients died awaiting liver transplantation from underlying liver disease and sepsis (none from underlying cardiac disease). 47 patients underwent liver transplant assessment but were not listed. 9 patients (19%) were not listed due to their underlying cardiac disease requiring intervention first, therefore leading to delay in listing for transplant. A further 16 patients (12%) were deemed unfit for transplant as a result of their underlying cardiac disease. 101/535 patients died (19%). 81% of the patients who died had not undergone liver transplantation. Leading causes of death were sepsis, chronic rejection in those transplanted and inoperable underlying disease. Cardiac disease was a reason for delay in transplant listing, with concerns regarding fluid shifts during transplantation being cited as primary reason for requiring cardiac intervention first.

Conclusion: Underlying cardiac disease is not uncommon in paediatric liver disease and poses a significant co-morbidity. This highlights the need for thorough cardiac assessment in all children presenting to tertiary hepatic services.

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Refractory ascites - safety of furosemide perfusion in a Pediatric Liver Unit

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Objectives and Study: Ascites is a frequent complication of cirrhosis. Diagnosis is based on clinical and /or ultrasound evaluation. Refractory ascites (RA), by definition, cannot be prevented by oral diuretics [1]. Large volume paracentesis is the second line treatment, often used in children. The use of furosemide continuous perfusion (FCP) was not reported in children. Concerns about its safety outside the ICU do exist. Our aim was to review the clinical experience of Pediatric Liver Unit with FCP.

Method: Descriptive analysis of episodes of refractory ascites treated with FCP in a low volume liver center, in the last 5 years. Refractory ascites were confirmed by ultrasound. Demographic and clinical data were collected. FCP doses started by 1 mg/kg/24h. Patients were continuously monitored for vital signs and daily for abdominal girth, weight, serum and urinary electrolytes. Patients with serum albumin < 27mg/dl received simultaneously albumin perfusion (AP).

Results: From the 94 episodes of ascites (34 patients), FCP was used in 15 (16%). Clinical diagnoses were: biliary atresia (n=9, 60%), unknown etiology (n=2, 25%), alfa-1 antitripsin deficiency (n=2, 13%), PFIC1 and portal vein thrombosis (n=1, 6.7%). Median dose/duration of FCP was 1.2 mg/kg/24h (min 0.72, max 2.4) / 10.2 days (1-23 days). AP was used in 93%. The median weight loss was 0.5%/day. Ascites resolved in 94% of episodes (14/15) under FCP during 4 days (median). Electrolyte imbalance occurred in 60% (9/15) of episodes: hypokaliaemia 2/15; hypofosfatemia 2/15. None patient had Na < 125mmol/L or ascending >10mmol/L during FCP. Median Na⁺ before FCP was 134mmol/L and after 138mmol/L. All electrolyte imbalance were easily corrected, with final median values: K 4.25mmol/L and P 1.73mmol/L. Hypotension occurred in 5/15 episodes.

Conclusion: Safety and efficacy of a low dose FCP for refractory ascites was demonstrated in this case series. Few complications were registered, the most frequent was electrolyte imbalance. No patient needed to be transferred to ICU. Basic monitoring makes the procedure feasible in a Liver Unit.

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Liver transplant as a treatment modality for Inflammatory myofibroblastic tumour

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Objectives and Study: Here, we report a case of inflammatory myofibroblastic tumor of liver extending into the IVC, right atrium and ventricle in a 3 year old female which was treated successfully with liver transplant, IVC & right atrium excision & reconstruction.

Methods: A 3 yr old female child presented with complaints of intermittent fever, abdominal pain, & abdominal distension for 3 months. CECT abdomen revealed a mass in the right hepatic lobe with thrombus in the IVC and right ventricle. Her CEA, Beta HCG and AFP were negative. She was hemodynamically stable & had firm hepatomegaly and pallor. PET CT abdomen revealed hypertrophied left lobe of the liver, FDG avid large heterogenous arterial enhancing lesion in the right lobe liver involving segment VII, VIII, VI with extension into IVC, right atrium and ventricle. She underwent a liver biopsy which was suggestive of inflammatory myofibroblastic tumor (bundles of oval to spindle shaped fibroblastic cells in a collagenized stroma with cells showing mild pleomorphism ). Immunohistochemical stain for ALK (Anaplastic Lymphoma Kinase) was positive but stain for SMA, CD34 and CD31 were negative). Crizotinib (ALK inhibitor) was started for reduction of the intracardiac tumor volume and patient improved. 3 months later ultrasound doppler revealed a lobulated hypoechoic mass involving the supra hepatic IVC (7.8 x 4.3 x 4 cm) extending into the right atrium. ECHO showed a localized mass in the RA filling the whole right atrial cavity and obstructing the IVC flow. The liver involvement was deemed non resectable due to tumor and secondary cirrhotic changes and hence the option of liver transplant along with cardiac clearance was considered. Living donor liver transplant with excision of the RA wall, IVC and Liver was planned. Intraop findings revealed a hard, lobulated externally palpable mass, totally obliterating the IVC and 90% of the RA volume. Tumor was excised along with the wide rim of RA and the IVC was excised from the RA. Posterior wall of the RA was reconstructed using autologous pericardium and a Y configured PTFE graft was used. The liver was explanted with the involved IVC, posterior limb of the graft was anastomosed to the supra renal IVC. The donor liver was then transplanted and hepatic artery anastomosis was done. She had uneventful stay in the Pediatric ICU for 13 days and was discharged on immunosuppression therapy after a total of 20 days in the hospital. She has been evaluated upto 6 months post transplant and is doing well.

Results: Inflammatory myofibroblastic tumors (IMT) are rare & occur in liver or lungs. Management of IMT is controversial. Some authors have advocated a conservative approach. However, the natural course of these tumors without intervention is not fully known. Importantly, when recurrences occur, it is usually in cases with incomplete resection and no chemotherapy.

Conclusion: Therefore, it is suggested that surgical resection should be recommended for all lesions if not prohibited by anatomic location or morbidity. In cases of anunresectable and metastatic ALK-expressing IMT, ALK inhibitors may provide therapeutic benefit with a shrinking tumor size. When completely resected with microscopically clear margins, IMFT can be curative, making surgical resection the mainstay of therapy.

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**HEPATOLOGY - Transplantation**

**H-P-133**

**Tacrolimus concentration/dose ratio is not associated with impaired renal function and acute cellular rejection after paediatric liver transplantation**

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**Objectives and Study:** Immunosuppression after organ transplantation is a complex issue. However, the adverse effects associated with immunosuppressant agents is a challenge for the clinician. Tacrolimus (TAC) is a cornerstone of immunosuppressive regimen in organ transplantation, including liver transplantation (LT). Recently it has been demonstrated in adult patients that the TAC concentration/dose ratio (serum level and daily dose - C/D) is associated with TAC nephrotoxicity. To the best of our knowledge, there are no published data on TAC C/D ratio in paediatric LT. We aimed to determine TAC C/D ratio in children underwent to LT and analyse the relationship between TAC C/D ratio, post-LT renal function and acute cellular rejection (ACR).

**Method:** We studied retrospectively children submitted to primary LT between Jan/99-Jul/16, who used TAC as immunosuppressor and had survived at least 30 days after surgery. Clinical and demographic data were assessed at transplantation and 5, 10, 15, 30, 90, 180 and 365 days after surgery. We studied the TAC C/D ratio distribution at 30th day after LT, and from this distribution we classified patients into three groups: slow, intermediate and fast metabolizers. We used percentiles distribution of C/D values in order to classify patients. TAC dose was compared between groups, during follow-up. We excluded missing data. Renal function was assessed by estimated glomerular filtration rate (eGFR) as described for Schwartz. Histological criteria or ALT>60 UI (no infections or vascular obstruction), responsive to immunosuppression adjustment defined ACR. Groups were compared by chi-square test of Pearson and generalized estimating equation model.

**Results:** We enrolled 105 patients. Fifty-six (53.6%) were male. Biliary atresia was the main transplant indication. Median age at transplantation was 3.5 years (p25: 1.50; p75: 10.50). TAC C/D was distributed asymmetrically. The median TAC C/D was 1.43 (p25=0.78 and p75=3.07). Twenty-six patients were classified as fast metabolizers (TAC C/D<0.78), twenty-six as slow (TAC C/D>3.07), and fifty-three as intermediate (TAC C/D between 0.78-3.07). TAC concentrations were significantly different among groups: slow metabolizers had higher TAC concentrations and fast had lower TAC concentrations. At five and ten days after LT, slow metabolizers presented a lower mean eGFR when compared to fast and intermediate metabolizers (p=0.002 and p=0.039, respectively). Except for these days, there were no significant difference of eGFR between groups (figure 1). Forty-one patients (39%) presented ACR (13 ALT criteria; 28 histological criteria). There was no significant difference between groups (p=0.29).
Figure 1: Estimated renal function measured by estimated glomerular filtration rate (Schwartz eGFR, mL/min) after LTx. Mean estimates and corresponding 95% confidence intervals from the multivariable linear mixed model according to groups of TAC C/D rate are plotted; overlapping areas are shown in confidence interval.

**Conclusion:** In children underwent to LT, TAC C/D was not associated with reduced Schwartz eGFR or ACR. More studies are needed to better understand the role of TAC C/D ratio on paediatric clinical practice.

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Headache following liver transplantation

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Objectives and Study: Post transplant headache is a recognized complication of organ transplantation presenting primarily or as a worsened previous migraine. The purpose of this study is to determine the prevalence of headache in patients after liver transplantation and assess the effect of suspected associated factors on its prevalence:

Method: A total of 100 patients undergone liver transplant between may 2015 and November 2016 were selected. A questionnaire was used to assess the patients' information retrospectively via both interview and chart review. The correlation between post transplant headache and associated factors including underlying condition contributing to transplant, immunosuppressive drugs, pre transplant MELD score & CHILD grade and post transplant elevated liver enzymes was then assessed by statistical analysis.

Results: 37 (37%) patients had experienced post transplant headache, among whom, it was newly formed in 20 (54.1%) patients. Patients with post transplant headache mostly had been confronted by episodes of headache when their liver enzymes were elevated (p-value=0.001). The relationship between other associated factors and post transplant headache was not statistically significant.

Conclusion: The elevated liver enzymes after transplantation seem to be an inducing or aggravating factor in patients who experience post transplant headache.
Electrocardiographic and echocardiographic findings in pre-liver transplant patients with Wilson's disease

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Objectives and Study: Wilson's cardiac involvement has been categorized as cardiomyopathy, arrhythmia, autonomic nervous system dysfunction, and sudden cardiac death. The purpose of this study was to assess the cardiac dysfunction in the pre-Liver Transplant Wilson patients and to stratify their risk of arrhythmia and sudden cardiac death:

Method: We enrolled 23 Wilson patients (candidate for Liver Transplant) and 47 healthy, age and gender matched participants in this case control study, which was carried out from 2012 to 2014 in the Transplant Coordination Center of Nemazee hospital. Cardiac function was evaluated by electrocardiography and echocardiography. P wave dispersion, QT dispersion and T peak to T end dispersion were measured and compared to the control group.

Results: P wave dispersion and QT dispersion were significantly increased in the Wilson patients (p<0.05). pulse Doppler echocardiogram findings showed significantly increased E, A peak velocity of mitral and tricuspid in Wilson patients (p<0.05). Tissue Doppler Imaging was in favor of significant increase of systolic and early and late diastolic velocity of Mitral and Tricuspid annulus.

Conclusion: Evaluation of Wilson's cardiac function should include Color Doppler and Tissue Doppler imaging to assess the diastolic dysfunction as one of the initial cardiac involvements.
Effectiveness, tolerability and safety of standardized milk-based, standardized non-milk based and hospital-based formulations in the management of moderate acute malnutrition in underfive children: A cluster randomized clinical trial

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Objectives and Study: Moderate acute malnutrition is a major contributor to under-five malnutrition-related mortality. There is presently no consensus on the appropriate nutritional formulation for managing this condition.

To determine the effectiveness, tolerability and safety of standardized milk-based, standardized non-milk based and hospital-based nutritional formulations for managing under-five children with moderate acute malnutrition.

Method: A cluster randomized clinical trial was conducted from April 2016 to May 2017. Children aged 6 to 59 months with moderate acute malnutrition were randomized to receive supplementary rations of standardized milk-based (SMBF), standardized non-milk based formulation (SNMBF) and hospital-based formulation (HBF) for four months. The participants received 50% of their daily caloric requirement for that period based on the intervention arm into which they were assigned. The effect of the formulations were assessed based on “per protocol” analysis using change in nutritional status as outcome measure. Approval for the conduct of the study was obtained from the University of Uyo Health Research Ethics Committee.

Results: A total of 687 children were screened for eligibility with 189 (27.5%) of them meeting the inclusion criteria. Of the eligible children, 70 were assigned to the SMBF group, 64 to the SNMBF group and 55 to the HBF group. There were 50/70 (71.0%), 54/64 (80.0%) and 37/55 (67.0%) evaluable participants in the SMBF group, SNMBF group and HBF group respectively. The overall recovery from moderate to mild acute malnutrition was 43 (86.0%) in the SMBF group, 42 (77.8%) in the SNMBF group and 29 (78.4%) in the HBF group. Catch up to normal nutritional status was attained by 7 (14.0%) children in the SMBF group, 5 (9.3%) in the SNMBF group and 2 (5.4%) in the HBF group. A case of deterioration from moderate to severe acute malnutrition was noted in the HBF group. Tolerability was comparable in all groups but report of skin rash was more in the SMBF group.

Conclusion: The different formulations were effective in managing under-fives with moderate acute malnutrition. However, the SMBF was slightly more effective than the SNMBF and the HBF. The formulations were well tolerated but there was more report of skin rash in the SMBF group.

Disclosure of interest: The study was sponsored by Nestle Nutrition. The comparators (standardized milk-based formulation and the standardized non-milk based formulation) were manufactured and supplied by Nestle Nutrition. However, the Organization (Nestle Nutrition) did not influence the design, conduct, interpretation of study results or report of the findings.

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Time of lactation and maternal fucosyltransferase polymorphisms are main determinants of human milk oligosaccharide variation.

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Rationale and Study: Human milk oligosaccharides (HMO) represent the third largest solid component of human milk after lactose and lipids. They are known to be affected by genetic variations on fucosyltransferases 2 and 3 (FUT2 and FUT3) and time. This study assessed changes in HMO levels during the first 12 months of lactation and the relationship with FUT2 (Secretor group defining) and FUT3 (Lewis group defining) genetic polymorphisms.

Method: Milk samples were collected from lactating mothers participating in the LIFE Child cohort in Leipzig, Germany. The concentrations of 23 HMO in milk samples collected at 3 months (N=156), 6 months (N=122) and 12 months (N=28) were measured using a validated high performance liquid chromatography method. Concentrations of individual and groups of HMO were compared at all time-points. DNA samples from mothers were used for sequencing FUT2 and FUT3 exonic regions to identify causal Single Nucleotide Polymorphisms (SNPs) that could influence enzyme functionality. The causal role of these SNPs was investigated by testing the associations between genotypes and average levels of HMO.

Results: FUT2 SNP rs601338 was found to predominantly define the Secretor status (Se+: 12.5%) and it was highly correlated with 2′-Fucosyllactose (2′FL) levels (P=0.8*10-21). FUT3 SNPs rs28362459 and rs812936 correlated with Lacto-N-fucosylpentaoase-II (LNFP II, P&LT; 10^-11) influencing the Lewis status in the population (Le+: 6%). The correlations remained similar over time. Secretor/Lewis status was associated with specific HMO profiles allowing us to define four milk types. Mean concentrations for the sum of the measured HMO as well as most individual HMO concentrations were lower at 6 and 12 months compared to 3 months (P<0.001). Especially, 3-Fucosyllactose (3FL) concentrations at 6 months increased by 35% compared to 3 months. Total, fucosylated and core HMO decreased throughout the 3 stages of lactation, whereas sialylated HMO first decreased from 3 to 6 months (predominantly driven by the decreasing concentration of 6’Sialyllactose, 6’SL) but increased from 6 to 12 months, driven by increasing concentrations of 3’Sialyllactose (3’S), Disialyllacto-N-tetraose (DSLNT) and Sialyllacto-N-tetraose b (LSTb).

Conclusion: We confirm by genetic analysis that 2′FL together with LNFP I and LNFP II are reliable proxies to define FUT2 (Secretor) and FUT3 (Lewis) status respectively. Despite the overall decrease in HMO concentration during the course of lactation, the concentrations of some HMO may increase. Further understanding of the factors controlling FUT2/FUT3 functionality could reveal regulatory mechanisms behind HMO expression and will help to better understand the temporal changes of HMO during lactation.

Disclosure of interest: Aristea Binia, Gregory Lefebvre, Aline Charpagne, Sean Austin and Norbert Sprenger are employees of Nestec.

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Objectives and Study: Feeding disorders of young children is a concern of many parents. As well as inappropriate habits, disturbed parent-child relationship, behavioral problems or ignorance of the principles of feeding, many studies indicate sensory processing difficulties as a crucial factor with feeding problems of children without underlying serious medical problems. Diagnosis process involves careful recognition of the full range of influences and indicates treatment approaches. The purpose of the present study was to identify problems and expectations reported by parents of children with feeding disorders.

Method: We performed a prospective study in children with feeding disorders referred to our hospital based on questionnaires completed by the parents before starting therapy (n=61; aged 24; HBD 38 weeks) and we compared it with the answers from the questionnaires completed by the parents of age matched children from public nurseries and kindergartens (n=58; aged 26; HBD 34 weeks). For the study we recruited children without underlying serious medical problems. We analyzed the following problems/components: the lack of appropriate weight gain (1), lack of hunger (2), acceptance to touch the food (3), choking during feeding (4), vomiting related to eating (5), holding food in mouth and refusal to swallow (6). We also looked at expectations of the parents related to the proposed therapy: increasing the amount of food digested by the child (7), increased diversity of food consumed (8), changing the texture of food (9), increasing the desire of the child to touch and explore the taste and smell of new food (10), improvement of eating behaviors (11). We compared problems and expectations of parents of children with feeding disorders(I) and problems and expectations of the control group(II) by chi square test, p<0.05 was considered as statistically significant.

Results: The frequency of problems and expectations reported by caregivers of healthy children with feeding disorders(I) and caregivers of controls(II) were as follows: (1) 13/47 vs 58/59; (2) 41/60 vs 55/59; (3) 37/61 vs 47/56; (4) 23/61 vs 0/59; (5) 16/61 vs 0/59; (6) 18/61 vs 1/59; (7) 40/61 vs 6/59 (8) 35/61 vs 12/59; (9) 23/61 vs 2/59; (10) 23/61 vs 5/59; (11) 26/61 vs 5/59. Statistically significant differences were found between two groups in components analyzed.

Conclusion: Expectations and problems related to child feeding reported by parents of children with feeding disorders and controls are different. The present study could provide data to identify problems with feeding young children.
Supplementation with *Lactobacillus rhamnosus* HN001 in early life prevents eczema throughout childhood

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**Objectives and Study:** Evidence is accumulating for a protective effect of some probiotics against the occurrence of eczema in infancy but is this effect maintained to later childhood? In a 2 centre randomized placebo controlled trial of *Lactobacillus rhamnosus* HN001 (HN001) (6 X 10⁹ colony forming units (cfu)) or *Bifidobacterium lactis* HN019 (HN019) (9 X 10⁹ cfu) taken daily from 35 weeks gestation to 6 months post-partum in mothers and from birth to age 2 years in infants, we showed that HN001 significantly protected against eczema development at 2, 4 and 6 years and atopic sensitization at 6 years. There was no effect of HN019. We report here the findings for the 12 month cumulative and point prevalence of allergic disease at 11 years.

**Method:** At age 11 years, we defined outcomes as both the 12 month prevalence and cumulative lifetime prevalence. Eczema was defined using the UK Working Party’s Diagnostic Criteria. Asthma, wheeze, hayfever and rhinitis were defined based on ISAAC questions. Atopic sensitization was defined as one or more positive responses (mean wheal diameter ≥ 3 mm) to a panel of allergens, including cat pelt, *Dermatophagoides pteronyssinus*, mixed grasses, egg white, peanut and cow’s milk, after subtraction of the negative control, and reported as both lifetime prevalence and point prevalence. The trial is registered at Australian New Zealand Clinical Trials Registry: ACTRN12607000518460, and approved by the Multi-Region Ethics Committee, New Zealand. An intention-to-treat analysis was used to assess probiotic effects on the 11 year cumulative prevalence using hazard ratios, and relative risks used to assess the 12 month prevalence of allergic disease at 11 years.

**Results:** At age 11 years, HN001 was associated with significant reductions in the 12 month prevalence of eczema (Odds ratio (OR)=0.46, 95% CI 0.25-0.86, p=0.01) and hayfever (OR=0.75, 95% CI 0.56-1.00, p=0.04). For the lifetime prevalence, HN001 was associated with a significant reduction in atopic sensitization (Hazard ratio (HR)=0.70, 95% CI 0.51-0.98, p=0.04) and eczema (HR=0.57, 95% CI 0.40-0.80, p=0.001). There was no effect of HN019 on these outcomes.

**Conclusion:** We are the first group to examine outcomes of a probiotic intervention to age 11 years. The persistent and long term effects of HN001 on eczema indicate that this simple intervention in early life has benefits that extend for many years into later childhood.

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Targeted probiotic supplementation reduces antibiotic resistance gene carriage in breastfed infants

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Objectives and Study: The increasing prevalence of ARGs is a growing public health concern. Commensal bacteria play a central role in the dissemination of antibiotic resistance genes (ARGs). Recent studies have focused on the early infant gut microbiome showing that ARGs are acquired in early life, even without antibiotic selective pressure, and may have long term sequelae. Currently, there are limited ways by which the spread of ARGs can be restricted that avoid the development of additional resistance mechanisms. Recently, we reported the effect of persistent and extensive gut microbiome modification by *Bifidobacterium longum subsp. infantis* EVC001 in breastfed infants. Here, we extend that analysis using shotgun metagenomics to examine the impact on these modifications on the total level of ARGs (i.e. the resistome).

Methods: Exclusively breastfed infants delivered vaginally or by cesarean section, were randomized to receive either lactation support and a novel commercial preparation of *Bifidobacterium longum subsp. infantis* (n=29) or lactation support alone (n=31). Infants consumed the preparation mixed with expressed breast milk for 21 days starting at day 7, and fecal samples were collected at day 21. Whole shotgun metagenomics was performed on an Illumina HiSeq 4000, and sequences were analyzed for the presence of antibiotic resistance genes using the Comprehensive Antibiotic Resistance Database (CARD).

Results: Infants fed *B. infantis* EVC001 were colonized in high levels by this strain of *Bifidobacterium* and had a significantly diminished abundance and diversity of ARGs. Particularly, infants fed EVC001 had, on average, 87.5% less ARGs in their microbiome (P&LT; 0.0001). Notably, 38 ARGs were significantly reduced in the supplemented infants. These genes are associated with resistance to a wide range of drugs including b-lactamase, fluoroquinolone and tetracycline. Furthermore, supplementation with EVC001 led to a reduction in both the relative and absolute abundance of *Escherichia*, who predominantly harbored ARGs.

Conclusion: Targeted bacterial supplementation capable of remodeling the community ecology of the infant gut microbiome may have evident clinical translation aspects, such as potential reduction of antibiotic resistance gene reservoirs. Thus, *B. infantis* EVC001 offers a novel approach towards an alternative, safe and non-invasive method with the potential to decrease a reservoir of a wide array of genes that confer resistance to clinically associated antibiotics. In concert with appropriate drug stewardship practices in the medical community, this approach of wholesale modulation of the gut microbiome could help reducing the burden and diversity of antibiotic resistance genes.

Disclosure of interest: GC, RMB, SAF and DV are employed by Evolve BioSystems, Inc. which funded the study.

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Body composition in preterm infants: changes over time and effect of nutrition in the early neonatal period (PeaPod study)

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Objectives and Study: Preterm infants are lighter and shorter, have more adipose tissue and less lean tissue than do term infants at the time of hospital discharge. Whether these differences in body composition persist to later age is not clear. Energy and protein supply in early postnatal period has been associated with body composition parameters. The aim of the PeaPod study was to: 1) prospectively assess body composition in preterm infants and term controls up to 4 months of age; 2) determine how nutritional factors affect body composition.

Methods: Premature infants (gestational week < 32 or birth weight < 2000g) and full-term healthy controls (37-41 weeks, 2500-4500 g) were recruited in a prospective longitudinal study in a tertiary care hospital in Umeå, Northern Sweden. All infants were followed until 4 months of age. Body composition (percentage body fat, fat mass, and fat free mass) was assessed by air displacement plethysmography (PeaPod Infant Body Composition System, Concord, California, USA) at four occasions (clinical stability, discharge, term-equivalent age, 4 months) in preterm infants, and at two occasions in controls (term and 4 months of age). Anthropometric measurements were performed at each occasion. Detailed data on nutritional intakes were retrospectively collected for the first 28 days of life.

Results: Thirty three preterm infants (mean gestational age 27.5 weeks) and sixty nine term controls were included. Preterms were significantly lighter and shorter compared to term infants at achieving term-equivalent age and at 4 months. At term equivalent age preterms had a greater percentage of fat mass [mean (SD): 20.17 (3.36) vs 11.67 (3.98); p<0.0001], higher fat mass [mean difference (MD) 0.26 kg; p&LT; 0.001], and lower fat free mass (MD -0.46 kg; p&LT; 0.001) compared to controls. Fat free mass remained lower in preterm infants at 4 months (MD -0.47 kg; p&LT; 0.001). Protein intake and protein-energy index (g protein per 100 kcal) at different time intervals were positively correlated with percentage of body fat and fat mass in univariate regression analysis. On the contrary, protein intake was a negative predictor of fat free mass at hospital discharge. After adjusting for gestational age and gender in a multivariate model, percentage of body fat was best predicted by gestational age and protein-energy index intake at week 2 (adjusted $R^2$ 0.47), fat mass by gestational age alone (adjusted $R^2$ 0.42). Protein intake at week 2 was the best (negative) predictor of fat free mass (adjusted $R^2$ 0.38).

Conclusions: Until 4 months of age preterm infants remained lighter and shorter compared to their term peers. At term equivalent age they had more adiposity and the deficit of fat free mass which persisted until 4 months. Accretion of adipose tissue was predicted by gestational age and higher protein intake at week 2. Surprisingly and unlike in the few studies published to date, protein intake was negatively associated to accretion of lean tissue. We are currently evaluating effect of nutritional intakes beyond 28 days of life on body composition until 4 months age.

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Nutrition and growth outcomes of children on enteral nutrition support completing an intensive weaning program

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Objectives and Study: Long-term enteral nutrition support (ENS) is often associated with negative side effects such as oral aversion, food refusal and perceived tube-dependency. We implemented a 3-week intensive tube-weaning program based on the Graz Model. The aim of this study was to examine the effect of the intervention on the nutritional status and growth of participating children over time.

Methods: Children age 0.5-12 years on long term ENS with complex medical histories and/or genetic syndromes, participated in a multidisciplinary weaning program. The professional team consisted of a paediatrician, dietitian, nurse, clinical psychologist, hydro-therapist and speech, physical, music and occupational therapists. The program was carried out in small groups of children who were predominately outpatients. The principles of the program were: 1) reduction of the tube feeding to promote hunger (2) a psychological-developmental approach to increase autonomy. One of the main interventions of the program called the “play picnic”, is a session of 60 minutes, once or twice a day, where different foods are served and the children are allowed to examine, touch and taste without parental interference. Acceptable weight loss during the process was considered to be up to 10% of the baseline body weight. Weaning could be complete (from 100% ENS to 100% oral) or partial (at least 80% reduction of ENS). Medical history along with nutrition and growth parameters were collected at baseline, after 3 weeks of the program, and 6 and 12 months after treatment. Data was converted to z-score values according to WHO growth standards.

Results: Fifty-eight children (64% boys), median age 2.8 (IQR: 3.27) years started the intervention program. Twenty-four children (42.1%) were born preterm, 45 (77.6%) suffered from developmental delay and 42 (75%) had eating problems from birth. Fifty-four (93%) completed the 3 week intensive weaning program. Weaning was achieved in 45 children (83%), with complete weaning in 22 (41%) and partial weaning in 23 (43%). No specific demographic or clinical predictors of success were identified i.e. age, gender, length of pregnancy, birth weight, medical diagnosis, anthropometric measurements or dietary factors. Average weight loss during the intervention was -5.22±3.7% (p< 0.001) of baseline weight, and mean energy intake was significantly reduced from 83% to 55% of recommended values (RDA). Currently, 37 out of the 45 weaned children (82%) have completed the 12-month follow-up. After 6 months significant reductions in weight-for-age z-scores were noted (-2.17±0.25 versus -1.38±0.23 SD) however, energy intake had returned to baseline levels. Stabilization of z-scores was achieved at 12 months.

Conclusions: This study provided additional evidence that an intensive multidisciplinary program, based on the Graz model can be used successfully in weaning children from tube-dependency. Short-term energy intake and weight loss were reversible and weight-for-age growth chart stabilized at 12 months. Further follow-up is recommended to ensure continued positive development in these children.

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Body composition and growth in children with intestinal failure receiving long-term parenteral nutrition

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**Objectives and Study:** Current growth monitoring and estimation of nutritional requirements of children with intestinal failure (IF) is mostly based on weight and height parameters and their evaluation over time. However, information about body composition of these children is not widely available. Our aim was to assess body composition of children with IF on long-term parenteral nutrition (PN) using air displacement plethysmography.

**Methods:** A cross-sectional study in children with IF who received PN for ≥ 6 months and were followed by a multidisciplinary IF team in 2 centers. Anthropometric assessment took place and body mass index (BMI), height for age (HFA), mid upper arm circumference (MUAC), weight for age (WFA) and weight for height (WFH) sex-specific standard deviation scores (SDS) were calculated with Dutch reference data. Body composition was assessed by using air displacement plethysmography with the BOD POD®, available for children >2 years of age. In contrast to other body composition methods, this method has no large inter-observer variability, and material such as the central venous catheter can be calibrated. Percent fat mass (%FM) and absolute fat free mass (FFM) SDS were estimated using Dutch reference values for these two parameters measured with DEXA (available >4 years of age). To determine whether growth and body composition differed significantly from that in the reference population, the Wilcoxon one-sample test was used.

**Results:** Twenty-two patients underwent body composition measurement at a median age of 7.2 years (range 2.1-16.8). Twelve patients had functional IF. Chronic intestinal pseudo-obstruction was the most common underlying disease (n=5). At time of measurement, 19 patients were still PN dependent. Median PN duration was 5.4 years (IQR 1.3-8.3 years). Patients with IF were significantly lighter (median WFA SDS -0.7, p=0.003) and shorter (median HFA SDS -1.3, p< 0.001) when compared to the reference population (Table 1). Ten patients (46%) were growing below their target height range. Median distance between actual HFA SDS and target height SDS was -0.9 (IQR -2.1-0.1, p = 0.001). For 19 patients %FM and FFM SDS could be calculated; patients had significantly more %FM (p< 0.001) and less FFM (p< 0.001) than the reference population. No significant differences were found according to PN dependency (full versus partial) or type of IF (surgical versus functional). Significant positive correlations were found between FFM SDS and all anthropometric parameters; WFA SDS (Spearman's rho 0.784, p< 0.001), HFA SDS (0.584, p=0.009), BMI SDS (0.558, p=0.013) and MUAC SDS (0.684, p=0.002). No significant correlations were found between SDS of the anthropometric parameters and %FM SDS.
At body composition measurement  n = 22, median age of 7.2 years median (IQR)  Compared to 0 SD (reference population)

Weight-for-age SDS  -0.7 (-1.5 to 0.0)  p = 0.003
Height-for-age SDS  -1.3 (-2.1 to -0.5)  p < 0.001
Weight-for-height SDS  0.1 (-0.4 to 0.8)  not significant
Body mass index SDS  0.1 (-0.6 to 0.7)  not significant
Mid upper arm circumference SDS  -0.5 (-1.7 to 0.3)  not significant
% fat mass  25.6 (18.7 to 31.0)  not applicable
% fat mass SDS  1.4 (1.1 to 1.9)  p < 0.001
Fat free mass (kg)  17.4 (13.5 to 22.8)  not applicable
Fat free mass SDS  -1.7 (-2.2 to -1.0)  p < 0.001

[Table 1 Growth and body composition assessment]

**Conclusion:** Despite close monitoring of weight and height and follow-up in a multidisciplinary team, children with IF on long term PN show significant abnormalities of body composition with higher FM and lower FFM compared to healthy children. Strikingly, WFH and BMI of these children were normal, suggesting that the use of these frequently used parameters is not valid in assessing FM in clinical practice. Further studies should evaluate the effect of a patient tailored approach including nutritional advice based on body composition together with advice regarding physical activity.

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Longitudinal analysis of butyrate in human milk: a GEHM study of three global cohorts through the first year of lactation

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Objectives and Study: Short chain fatty acids (SCFA), in particular Butyrate (C4:0), are increasingly recognized to have beneficial physiological effects and have recently been detected in human milk through metabolomics studies. However, butyrate levels in milk are not well established and variation between regions and across lactation are unknown. Therefore, the objective of the current study was to provide a longitudinal assessment of total butyrate concentrations in human milk across the first year of lactation from mothers in three globally diverse cohorts.

Methods: Human milk was collected from mother-infant pairs participating in the Global Exploration of Human Milk (GEHM) study from three global populations in Shanghai, China, Mexico City, Mexico, and Cincinnati, United States. Longitudinal series of milk samples (2, 4, 13, 26 and 52 weeks of lactation) were analyzed from 10 mothers from each region (n = 150 samples from 30 mothers). Butyrate quantification was performed by measuring butyric acid (BA) using a newly developed gas chromatography-mass spectrometry method utilizing a lipase assisted sample preparation. Development of an accurate BA analysis was a critical step in this study due to the volatile nature of SCFA and required the use of deuterated butyric acid (BA-D7) as an internal standard to improve recovery and precision. The analytical approach was fully validated to ensure optimal precision and accuracy before evaluating human milk samples.

Results: Milk from distinct geographic regions exhibited similar total butyrate concentrations as well as temporal patterns between 2 and 52 weeks of lactation. ANOVA analyses using a factorial design for location, week, donor, and the location by lactation stage interaction indicated that butyrate levels increased over lactation (p < 0.001). Butyrate content was associated with donors (p < 0.046), although no association amongst regions or location by lactation stage interaction was identified. Due to the lack of association with regional butyrate levels, averages were determined across the whole population per week of lactation. Mean butyrate levels increased over lactation from 8.5 µg/mL at 2 weeks to 18.6 µg/mL at week 13 then plateaued to 52 weeks at 19.5 µg/mL. Overall, the median total butyrate content of human milk across all countries and lactation stages was 14.2 µg/mL with an interquartile range of 8.5 - 20.3 µg/mL.

Conclusion: This longitudinal study presents a global glimpse into the butyrate content of human milk through the first year of lactation. Data generated from this study proposes butyrate concentrations are consistent across regions. Human milk butyrate being donor dependent may suggest that maternal diet influences overall levels. Additionally, butyrate concentrations increasing over lactation align with recent human milk metabolomics studies where mature milk was semi-quantitatively identified to contain higher butyrate levels than colostrum or transitional milk.


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Longitudinal evolution of major protein concentration in preterm and term human milk

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Objectives and Study: Proteins are major contributors to the beneficial effects of human milk (HM) on preterm infant health and development. Alpha-lactalbumin, lactoferrin, serum albumin and caseins represent approximately 85% of the total protein in HM. The longitudinal evolution of these proteins in preterm (PT) HM and its comparison with term (T) HM is poorly characterized.

This study aimed at quantifying and comparing the content of major HM proteins from milk of mothers delivering term and preterm infants along stages of lactation.

Method: HM from mothers who delivered prematurely (28 0/7-32 6/7 of gestation, n=25) and who delivered at term (37 0/7-41 6/7 of gestation, n=26) was collected for 4 months postpartum at 12 time points for PT HM (280 samples) and for 2 months postpartum at 8 time points for T HM (220 samples). Samples were collected from the first, single full breast expression in the morning. Proteins were measured by using a micro-fluidic LabChip system.

Results: Casein, alpha-lactalbumin and lactoferrin contents decreased with advancing stages of lactation in PT and T HM, whereas serum albumin remained stable during the study period. Only marginal differences between PT and T HM were observed for alpha-lactalbumin during postpartum weeks 3-5 and for serum albumin at the first week. By contrast, a comparison of PT and T HM provided to preterm and term infants at the same postmenstrual ages revealed that alpha-lactalbumin contents were significantly lower in PT HM than in T HM during the 39-48 postmenstrual weeks.

Conclusion: This study provides comprehensive information of the longitudinal changes of major proteins in preterm milk, and suggest limited availability of alpha-lactalbumin, a nutritionally important protein, in breastfed preterm infants after reaching the term corrected age. This information could be important to increase the accuracy of HM protein fortification, although its relevance needs to be confirmed by future intervention trials.

Disclosure of interest: CLGR, CADC, RJ, SKT and MA are all employees of Nestec Ltd. LB, JFT, CJFF declare no conflict of interest beyond the grant received from the Nestle Research Center for conducting this study

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Osteopontin levels in human milk vary across countries and within lactation period: Data from a multicenter study

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Objectives and Study: Osteopontin (OPN) is a multifunctional protein expressed in many cell types, tissues and body fluids with the highest concentrations found in milk; higher in human than in bovine milk. Intervention studies have indicated beneficial effects of supplementing infant formula with bovine OPN. However, current knowledge on the OPN level in human breast milk is based on small studies comprising few mothers. In this explorative, multicenter study, we aimed to investigate the OPN content in a large number of human breast milk samples from four different countries; China, Denmark, Japan and Republic of Korea.

Method: Due to ethical and legal conditions, the OPN and macronutrients analyses were performed at each of the four study locations, whereas data management and statistical analyses were conducted in Denmark. In China, mothers were seen 30, 60 and 90 days postpartum. In Denmark, mothers in the Odense Child Cohort were seen three months postpartum. In Japan, mothers in the Japanese Human Milk Study were seen one month postpartum. In Republic of Korea, mothers from postpartum care centers, baby fairs and breastfeeding seminars were seen five weeks postpartum. OPN was measured using a commercially available ELISA kit validated for quantitative determination of OPN in human breast milk. A mid-infrared transmission spectroscopy device (Miris Human Milk Analyzer, Sweden) or a Fourier transformation infrared spectroscopy device (MilkoScan FT2, Foss Analytical, Denmark) developed for in-hospital macronutrients analysis of human breast milk was used to determine the protein concentration. Data are presented as mean and standard deviation (SD) if normally distributed, otherwise as median and interquartile range (IQR).

Results: A total of 829 breast milk samples from 629 mothers were included, i.e. 521 mothers delivered one sample, 16 delivered two and 92 delivered three samples. When delivering the first sample, mean maternal and median infant age were 31.4 years (SD = 4.0) and 13.4 weeks (IQR 4.6-17.9), respectively. The median OPN concentration varied across sites; from 99.7 mg/L in Danish, 182.5 mg/L in Japanese, 216.2 mg/L in Korean to 266.2 mg/L in Chinese mothers, corresponding to 1.3%, 2.4%, 1.8% and 2.7% of the total protein content (OPN/protein%), respectively. Based on the 108 mothers delivering more than one sample, a mixed model regression analysis showed a decrease in OPN concentration with infant age ($\beta = (-5.9)$, 95% confidence interval = (-7.4)-(-4.4)).

Conclusion: In this large multicenter study, we observed significant differences in the OPN concentration and the OPN/protein% in human milk samples across countries and within the lactation period. A significant decrease in the OPN concentration with infant age was observed. The decrease in OPN concentration with infant age was more pronounced within the Chinese samples, collected from 4-13 weeks of age compared to the Japanese collected from 8-25 weeks of age.
Disclosure of interest: The study was supported in parts by Arla Foods Ingredients Group P/S, Biostime Health Products Ltd., Mael Dairies Co., Ltd., and Bean Stalk Snow Co., Ltd. Arla Foods Ingredients Group P/S holds a patent on the use of bovine milk osteopontin in infant formula. ESS is among the inventors of this patent.

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Body composition of infants fed goat-milk infant formula vs. cow-milk infant formula: a randomised controlled trial

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Objectives and Study: We previously showed no difference in growth (measured by weight, length and head circumference) between infants fed goat-milk infant formula containing milk fat and those fed a conventional cow-milk infant formula without milk fat in a randomised controlled trial (the TIGGA trial). In this study, we compared body composition of the two groups of formula-fed infants in the TIGGA trial. We also compared body composition of formula-fed vs. breastfed infants.

Methods: 200 formula-fed term infants were randomly assigned to goat-milk or cow-milk infant formula in the first 12 months of age. A reference group of 101 breastfed infants were included for comparison. Fat mass (FM) and fat free mass (FFM) were measured at 1, 2, 3, 4, 6 and 12 months using bioimpedance spectroscopy (BIS).

Results: The mean (SD) FM ranged from 682 (184)g at one month to 3022 (555)g at 12 months in the goat-milk formula group compared with 728 (178)g to 3116 (565)g in the cow-milk formula group. The mean (SD) FM% ranged from 16 (3)% to 31 (4)% in the goat-milk formula group compared with 17 (3)% and 31 (3)% for the cow-milk formula group. There were no differences between the two formula groups in FM and FM%, or FFM and FFM%, at any time points. Overall, formula-fed infants had a higher mean FFM at four months [mean difference (MD): 160g, 95% CI: 50.4, 269.5g, p<LT; 0.05)], and six months (MD: 179g, 95% CI: 41.5, 316.9g, p<LT; 0.05) compared with the breast-fed infants. However, by 12 months mean FFM between formula-fed and breastfed infants was not significantly different. Subgroup analysis of breastfed vs. formula-fed infants by maternal smoking status in pregnancy showed that there were no differences in the FM, FM%, FFM and FFM% between the breastfed and formula-fed infants whose mothers did not smoke in pregnancy. Formula-fed infants whose mothers smoked in pregnancy had lower FM and FM%, and higher FFM and FFM% at one month compared with infants of non-smoking mothers regardless of feeding mode, but the differences were not significant at other time points.

Conclusion: Body composition of infants fed goat-milk infant formula did not differ from those fed cow-milk infant formula. Differences in body composition between breastfed and formula-fed infants may partly be due to maternal smoking in pregnancy, independent of the feeding mode in infancy.

Disclosure of interest: Makrides serves on scientific advisory boards for Nestle and Fonterra. Gibson serves on scientific advisory board for Fonterra. Associated honoraria for Makrides and Gibson are paid to their institutions to support conference travel and continuing education for post-graduate students and early career researchers. Prosser is employed by Dairy Goat Co-operative (N.Z.) Ltd, New Zealand who funded the study. All other authors declare no conflicts of interest.

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A partly fermented infant formula with prebiotics scGOS/lcFOS modulates the gut microbiota functioning towards a more breastfed-like microbiota

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Objectives and Study: To investigate the efficacy of a partly fermented infant formula combined with scGOS/lcFOS (0.8 g/100 ml, 9:1) compared to a control product (without prebiotics or ferment) on the fecal microbiota composition and functioning. To place the microbiota differences in context, the same parameters were determined in a breast-fed reference arm within the same clinical trial (registered under Netherlands Trial registry NTR3455). In each of the three study arms stool samples were collected on the day of randomization or the day thereafter (0-4 weeks of age), during the intervention (8 weeks of age), and at the end of intervention (17 weeks of age).

Method: For a subset of 30 vaginally delivered subjects with a complete sample set per study arm, first targeted physiological parameters (such as pH, levels of short chain fatty acids, and levels of sIgA) were assessed. Next, microbial community composition was determined by specific Q-PCR assays and by untargeted 16S rRNA gene amplicon sequencing. Finally, to characterize microbial function in more detail, for approximately 20 subjects per study arm all stool samples were subjected to untargeted metabolomics.

Results: During and at the end of intervention the infants consuming the partly fermented formula showed, in contrast to the infants consuming the control product, a saccharolytic fermentation profile (e.g. lower pH, higher levels of acetic acid and sIgA, increased Bifidobacterium sp, and decreased Clostridium difficile occurrence). Pyrosequencing showed that the partly fermented formula did not change the entire microbiota community. However, various bacterial taxa (4-11 genera, depending on the time point) did change consistently when comparing partly fermented with control formula. These changes were in line with prebiotic effects observed with the physiological parameters. At the end of intervention, the levels of these differential bacterial groups in the experimental arm appeared to be more in line with the levels detected in the breast-fed reference arm. In contrast to the pyrosequencing data, the metabolomics data showed much more and larger differences between the study groups at nearly every time point (180 - 404 metabolites per comparison). At baseline the experimental and control arm were relatively close to one other. The significantly different metabolites represented numerous functional categories. This untargeted data set illustrates that infant gut ecosystem functioning is highly dependent on and reactive to the diet. Interestingly, in time the experimental arm deviated less from the breastfed reference arm as compared to the control arm.

Conclusion: The characteristics of the fecal samples in this study reflected that the infants consuming the partly fermented formula have a more breastfed like microbiota composition and physiological conditions in the gut as compared to the control group. Moreover, the more in depth untargeted analyses showed that the gut microbiota functioning in infants on partly fermented formula deviates less from the breastfed reference group than in infants on control formula, suggesting that the partly fermented formula drives the gut ecosystem towards a more breastfed-like situation.
Disclosure of interest: ST, JP, GR and JK are employees of Danone Nutricia Early Life Nutrition, which funded the study.

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Maternal effects on sleep/wake patterns in infants receiving a cow's milk-based infant formula with a prebiotic blend

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Objectives and Study: Infant sleep/wake patterns undergo rapid nocturnal sleep consolidation and maturation of wake rhythm during the first 6 months of age. Few studies have documented the nutritive effects of prebiotics on infant sleep/wake cycle progression as early behavioral indicators of tolerance. In addition, evidence of potential bidirectional interactions between the microbiome, gut and brain are also emerging. The effects of diet on sleep-wake entrainment, and gut-brain axis connections require further study.

Method: This multi-center, double-blind, controlled, parallel-group, prospective pilot study tracked longitudinal development of 24-h sleep/wake organization in healthy term infants randomized to receive one of two formulas from baseline (14-35 days of age) up to 112 days of age: routine cow's milk-based infant formula without added prebiotics (Control; n=82) or with prebiotic ingredients (polydextrose [PDX] and galactooligosaccharides [GOS]; 4 g/L, 1:1 ratio) (PDX/GOS; n=79). Infants wore actigraph devices at three study timepoints (consecutive 72-h periods at baseline, Day 70, and Day 112) which continuously recorded movement and rest. Motor activity data were digitalized, stored for each successive 1-min interval, and divided into nocturnal and diurnal (daytime) periods; 24-h sleep-wake variables were averaged from collected motor activity data and analyzed by repeated measures ANOVA.

Results: A total of 131 infants completed the study. Complete actigraphy data (all study timepoints) were available for 124 participants. Significant age-related changes were demonstrated by study end (P≤0.018): total nocturnal time awake and mean duration of wake episodes decreased; total diurnal wake time increased and both number and duration of naps decreased. In addition, significantly longer latency to first and second nap since wake-up time (hours, mean ± SE) was observed for the PDX/GOS compared to the Control group at Day 112 (Figure).
Conclusion: Results indicate faster consolidation of daytime waking state in infants receiving prebiotics and provide further support for home-based actigraphy to assess sleep/wake patterns throughout the first months of life. The effect of prebiotics on wake organization is consistent with an influence on the gut-brain axis and requires further study.

Disclosure of interest: This research was funded by Mead Johnson Nutrition. In addition, I serve as an occasional consultant to Mead Johnson Nutrition.

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**Human milk oligosaccharides profiles from healthy European mothers: New insights from Atlas of human milk nutrients, a multicenter observational cohort**

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**Rationale and Study:** Human milk oligosaccharides (HMO) vary between mothers and change over lactation. Their variability may be an indicator of maternal health and due to their multifunctionality they might impact infant growth and development. We explored whether maternal pre-pregnancy Body Mass Index (ppBMI), Gestational Weight Gain (GWG) and age, may affect HMO concentration.

**Method:** The Atlas of Human Milk Nutrients study included 370 healthy mothers of any ethnicity enrolled across 7 European countries. Information on maternal age, gestational age at birth, ppBMI and GWG were recorded. Human milk samples were collected during mid-morning at 2, 17, 30, 60, 90 and 120 days post-partum after complete expression of one breast. Concentrations of 23 HMOs were measured using a validated ultra-high performance liquid chromatography. Associations of each of these maternal characteristics with individual HMO levels were studied using mixed linear models.

**Results:** Overweight women, based on pre-pregnancy BMI (≥25 and ≤29.9), had higher levels of sialylated HMO, and of Disialyllacto-N-tetraose (DSLNT) at day 2 (MD: 53 mg/L, P=0.01) compared to normal weight women, whereas 3'SL was higher in normal weight women at day 60, 90, 120 (MD: 12 mg/L, P&LT: 0.05). Higher GWG (11.3-15.8 kg) was associated with higher levels of 3'SL, DSLNT and LNFP-III at day 2 (MD: 28, 83, 69 mg/L respectively, P&LT: 0.001 for all) compared to lower GWG (6.8-11.3 kg). There were no significant associations between maternal age and individual HMO levels. No significant differences were seen for pre-pregnancy BMI, GWG and other abundant HMOs that we measured. We detected no significant relations between maternal age and individual HMO levels.

**Conclusion:** Pre-pregnancy BMI and GWG may influence individual HMO levels as was recently suggested, albeit the effects on their concentrations are generally small. The clinical relevance of these subtle differences in HMO levels need to be evaluated in future longitudinal cohorts of mothers and infants. Results from these future studies will provide insight on the interactions between both maternal and infant characteristics with HMO to understand their role in maternal and infant health.

**Disclosure of interest:** Aristea Binia, Tinu Mary Samuel, Carlos Antonio de Castro, Irma Silva Zolezzi, Sagar K. Thakkar, Sean Austin, Norbert Sprenger are Nestec employees.

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Utilization of human milk oligosaccharide 2'-fucosyllactose by various probiotic strains and characterization of gene clusters involved in HMO metabolism by Bifidobacterium longum ssp. infantis Bi-26

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Objectives and Study: Human milk oligosaccharides (HMOs) are prebiotics that support for instance digestive, immune and cognitive health in infants. They are not digested by infants but are metabolized by beneficial bacteria such as Bifidobacterium species hence shaping the intestinal microbiota. Bifidobacterium longum ssp. infantis and Bifidobacterium bifidum are the major HMO consumers found in breastfed infant feces. However, most gastro-intestinal bacteria do not grow well using HMOs as a sole carbon source. We evaluated the ability of various species of Lactobacillus, Bifidobacterium and Bacteroides as well as some potentially pathogenic bacteria to ferment HMO 2'-fucosyllactose (2'-FL), glucose, lactose or galacto-oligosaccharide (GOS) as a sole carbon source. Since there is limited knowledge of how specific Bifidobacterium strains utilize individual HMOs, we performed transcriptomics analysis of B. longum ssp. infantis Bi-26 strain during growth with 2'-FL as a carbon source.

Methods: Bacterial growth was monitored by measuring the absorbance at 600 nm every 30 min for 24 h using the automatic Bioscreen© C system under anaerobic conditions using optimal culture media for each bacterial strain containing 1% 2'-FL, glucose, lactose or GOS as a sole carbon source. Transcriptomic data was obtained by growing B. longum ssp. infantis Bi-26 in modified Bifidobacterium Media 58 (DSMZ) containing 1% 2'-FL, lactose or GOS. Samples were taken at early phase (A600 0.25), at mid log (A600 0.5-0.7) and at late log (A600 0.9-1.1), centrifuged and suspended in trizole. After RNA isolation and treatment, samples were sequenced via HiSeq®2500 (Illumina) with a read length of 76bp (paired ends). Genomic analysis was performed with DNASTAR®.

Results: Only certain bifidobacteria, such as B. longum ssp. infantis and B. bifidum as well as Bacteroides fragilis and Bacteroides thetaiotaomicron strains utilized 2'-FL as a sole carbon source, while almost all tested strains of bacteria were able to consume glucose, lactose and GOS, highlighting the specificity of 2'-FL as an energy source for the beneficial bacteria. The results revealed that several novel gene clusters were involved in the breakdown and transport of 2'-FL, and that the metabolism of 2'-FL is a complex process involving multiple gene clusters throughout the genome compared to the lactose and GOS controls.

Conclusions: These results show the selectivity in 2'-FL utilization between different Bifidobacterium strains, and the mode-of-action of 2'-FL metabolism by Bi-26. This data could be used to further determine the genetic and functional properties of probiotic-HMO interactions.

Disclosure of interest: All authors are employees of DuPont Nutrition & Health, which manufactures and sells 2'-fucosyllactose and Bifidobacterium longum ssp. infantis Bi-26 probiotic product.

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Iron fortification may reduce efficacy of oral antibiotics against enteropathogens, whereas galacto-oligosaccharides (GOS) mitigate the adverse effects of iron fortification on the gut microbiome in Kenyan infants

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Objectives and Study: Anaemia due to iron deficiency is highly prevalent in African infants. Iron-containing micronutrient powders (MNPs) can reduce anaemia, but iron may decrease gut Bifidobacteriaceae and Lactobacillaceae, and increase enteropathogens, diarrhoea and respiratory tract infections (RTIs). We evaluated the efficacy and safety of a new MNP with prebiotic galactooligosaccharides (GOS) combined with a low dose (5 mg/day) highly bioavailable iron. GOS is expected to counteract the adverse effects of iron on the gut microbiota. Secondly, antibiotics are one of the most commonly prescribed medications for African infants. At the time of peak use of antibiotics, many infants are also receiving iron fortificants to prevent iron deficiency anaemia. Antibiotic efficacy against enteropathogens may be modified by high colonic iron concentration. We therefore evaluated the effect of antibiotic treatment on the gut microbiota composition during MNP-iron fortification in a subset of infants.

Methods: Kenyan infants aged 6.5-9.5 months (n=155) were randomized to receive a daily dose of (1) a MNP without iron (control; Fe-); (2) the same MNP but with 5 mg iron (Fe+); or (3) the identical MNP as the Fe+ group but with 7.5 g GOS (Fe+GOS) during 4 months. Primary readouts were gut microbiota composition assessed by 16S rRNA gene Illumina sequencing and qPCR, gut inflammation as measured by fecal calprotectin and plasma Intestinal Fatty Acid Binding protein (IFAB-P; a marker for enterocyte damage). Secondary readouts were anaemia status and morbidity. In the antibiotic substudy, from 28 infants in four groups (Fe Ab-, Fe Ab+, Fe+Ab-, Fe+Ab+) fecal samples were collected on days 0, 5, 10, 20 and 40; antibiotic cases were treated for 5 days after sampling at d0.

Results: Anaemia decreased by ~50% in the Fe+ and Fe+GOS groups (p&LT; 0.001). Compared with Fe or Fe+GOS, in the Fe+ group (1) lower abundances of Bifidobacterium and Lactobacillus and higher abundances of Clostridiales (p&LT; 0.01); (2) higher abundances of virulence and toxin genes (VTGs) of pathogens (p&LT; 0.01); (3) higher plasma IFAB-P (p&LT; 0.05); and (4) a higher incidence of treated RTIs (p&LT; 0.05) were found. In contrast, no significant differences were found when comparing Fe+ with Fe+GOS, with the exception that the abundance of VTGs of all pathogens was significantly lower in the Fe+GOS group (p&LT; 0.01). In Fe Ab+, from D0 to D5 and D40, there was a decrease in pathogenic E. coli and the sum of total pathogens (for all, p&LT; 0.05), but no decrease in Fe-Ab+. In Fe-Ab+ from D0-D5, there was an increase in C. difficile in 5 of 7 infants, but no increase in Fe Ab+. In Fe-Ab+, from D0 to D5 and D40, there was a decrease in Bifidobacteriaceae, while they increased in Fe Ab+ (for both, p&LT; 0.05).

Conclusion: The MNP containing a low dose of highly bioavailable iron successfully reduces anaemia, and the addition of GOS mitigates most of the adverse effects of iron on the gut microbiome and morbidity in African infants. The antibiotic substudy shows that iron fortification modifies the response to oral broad-spectrum antibiotics, promotes C. difficile growth, and may inhibit the bactericidal effect of antibiotics against potential enteropathogens, particularly pathogenic E. coli.

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Administration of iron as drops has significant effects on the gut microflora of iron-sufficient infants: a randomized controlled study

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Objectives and Study: Apart from being an essential nutrient, iron also plays an important role in the colonization and virulence of many bacteria in the human gut. Previous trials have reported adverse effects of iron fortification on the gut microbiota of children with iron deficiency. The aim of the present study was to assess the safety of iron fortification by investigating putative changes in gut microbial composition in healthy, iron-sufficient infants. Infants at 6 mo of age were randomly allocated to receive a low iron-fortified formula (providing 1.2 mg Fe/d), a high iron-fortified formula (providing 6.6 mg Fe/d) or an iron-unfortified formula with supplementation of iron as drops (iron drops; providing a total of 6.6 mg Fe/d from the iron-unfortified formula and the iron drops). The intervention lasted 45 days and stool samples were collected before and after the intervention.

Method: We applied 16S rRNA gene amplicon sequencing of the V3-V4 region to profile the gut microbiome using Illumina MiSeq. The composition and diversity of the gut microbiome were assessed using Quantitative Insights into Microbial Ecology (QIIME), generating 561 operational taxonomic units (OTUs). The DESeq2 package was used to investigate differences in relative abundance of gut bacteria among the groups. Phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt) was used to predict metagenome functional content using observed 16S rRNA frequencies. Spearman’s rho was used to test associations between composition of gut microbiota (OTUs) and faecal calprotectin concentrations. Statistical analyses were performed using R 3.4.1 and SPSS version 23.

Results: From 72 enrolled infants, 52 vaginally delivered infants with paired stool samples were included for analyses. Compared to the low iron-fortified formula group, the high iron-fortified formula group had lower abundance of Blifidobacterium (p&LT; 0.001) but higher abundance of Bacteroides (p&LT; 0.001) and Lactobacillus (p&LT; 0.0002). When comparing the high iron-fortified formula group to the iron drops, the latter group had lower abundance of Lactobacillus (p&LT; 0.007) and Streptococcus (p&LT; 0.0003) but higher abundance of Clostridium (p&LT; 0.05) and Bacteroides (p&LT; 0.02). Faecal calprotectin was associated with a higher relative abundance of Clostridium difficile in the high iron-fortified formula group (rs = 0.40, p&LT; 0.01) and iron drops group (rs = 0.48, p&LT; 0.004), but not in the low iron-fortified formula group. Assessing the functional content of the gut bacteria, we found that the bacterial functional pathway related to responses to S. aureus infection was significantly reduced in the iron drops group compared to the low iron-fortified formula group (p&LT; 0.03).

Conclusion: In these iron-sufficient infants, a dose of 6.6 mg Fe/day for 45 days was sufficient to induce significant changes in gut microbial composition compared to infants receiving 1.2 mg Fe/d. Administration of iron as drops had a larger and potentially more unfavourable effect on gut microflora compared to infants fed iron-fortified formula.

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N-O-019

A single intake of a polysaccharides mix reduces postprandial triglycerides, ghrelin and appetite in obese children: a clinical trial

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Objectives and Study: The aim of this study is to test the hypothesis that a single intake of a polysaccharides mix (Policaptil Gel Retard) is able, in comparison with placebo, to affect metabolic and hormonal postprandial profile and to reduce appetite in obese children.

Method: 40 obese children were recruited. Subjects were randomly assigned to treatment with Policaptil Gel Retard (Group A) or placebo (Group B), in a double blind clinical trial. Weight, height and waist circumference were measured by standard methods and body composition was assessed by bioimpedance. Two Policaptil Gel Retard tablets or placebo were given at 08:00 a.m. in fasting condition, 20 minutes before the ingestion of a mixed meal (15 kcal per kg of lean body mass: protein 12%, lipid 35%, carbohydrate 53%). Blood samples were taken at baseline and at 30-minute intervals for the first two hours and 60-minute intervals for the following two hours in the postprandial phase, for a total of 4 hours, for measuring blood lipids, glucose, insulin, ghrelin, and GLP-1. Pre- and postprandial appetite was quantified, at the same intervals, by a visual analog scale.

Results: The physical characteristics were comparable in the two groups. Children assuming Policaptil Gel Retard had a significantly lower postprandial increase of triglycerides (triglycerides AUC: 2,695(2,791) vs 5,112(3,891) mg*dl\(^{-1}\)*240'; P=0.033) and ghrelin (ghrelin AUC: -8,886(8,319) vs -4,278(5,024) pg*mL\(^{-1}\)*240'; P=0.048) and a higher decrease in appetite (appetite AUC: -264(287) vs 54(338); P=0.004), than children assuming placebo. Blood glucose, NEFA, insulin and GLP-1 profiles were not significantly different in the two groups. A significant correlation between appetite AUC and ghrelin AUC was also found (r=0.34, P=0.04).

Conclusion: A single intake of 2 tablets of Policaptil Gel Retard was associated with a significant reduction of appetite, ghrelin, and triglycerides in a 4-h postprandial period in obese children. No acute effects on glucose metabolism were detected. The reduction of the appetite and of the postprandial exposition to high levels of triglycerides could be useful for weight and cardiovascular risk reduction in the treatment of childhood obesity.

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The Cow Milk Symptom Score (CoMiSS™) in healthy infants

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Objectives and Study: A group of experts published in 2015 a workshop report on the development of a Cow’s Milk-related Symptom Score (CoMiSS™) as an awareness tool. The CoMiSS includes symptoms on regurgitation, stool composition, skin manifestations, respiratory symptoms and crying time and has a range between 0 and 33. Arbitrary, a cut-off of ≥12 was defined as a “positive score”. Trials showed systematically a significant decrease of the score during elimination diet and an increase during challenge. However, as a consequence, the question did arise what the level of CoMiSS would be in healthy infants.

Method: General paediatricians determined CoMiSS in healthy infants < 6 months of age during a routine visit. Infants had to be “healthy”, meaning that parents did not consult because of any symptom or sign. Exclusion criteria were: therapeutic formula, administration of any food supplement (except the recommended vitamins) or medication, preterm (< 37 weeks), >6 months of age. The following information was acquired: gestational age, gender, age < 6 months, breast or formula feeding. The different categories from the CoMiSS score (crying, regurgitation, stool composition, skin, respiratory symptoms) were also collected. The scores were registered anonymously. There was no funding for this study. Ethical approval was obtained.

Results: Data from 809 infants were collected. Complete information was obtained from 333 infants (Belgium: 128 (38.4%), Italy: 75 (22.5%), Spain 130 (39.0%). Exclusions: extensive hydrolysate (n:3), prematurity (n:8), age > 6 months (n:31), gender missing (n:170), no information on type of feeding (n:264). In all 333 infants, the CoMiSS was < 12. In the 333 infants, the mean and median CoMiSS were 2.77 and 2.83, respectively (Figure 1; Table 1). 86.6 % had a CoMiSS ≤6 and 94.6 % ≤8. CoMiSS seems age dependent (CoMiSS vs age monthly age class: H(2)=16.3,p=0.006), mainly because healthy infants cry more at the age of 2-3 months (monthly age class vs crying score: H(2)=13.7, p=0.018). Infants also regurgitate more when older than one month compared to those of 1-2, 2-3 and 3-4 months (p values ≤0.010), but not compared with those between 4-5 (p=0.686) and 5-6 months (p=0.188). The other components of the CoMiSS were not age dependent. In the 333 infants with the complete data set, gender (p=0.711) and type of feeding (breast vs formula) (p=0.757) had no influence on the CoMiSS. Therefore, the data were re-calculated including those infants with gender and type of feeding missing (n: 738). In this group, mean and median CoMiSS were 3.88 and 4.00, respectively (Figure 1); the CoMiSS was ≥ 12 in 14/739 (1.9 %). Outcomes remained identical for CoMiSS vs crying score (p< 0.001), but changed for regurgitation vs age (p=0.078).
Conclusion: In healthy infants < 6 months, median CoMiSS is 2.83. The analysis of the data suggests that a cut-off of ≥9 might be better performing than the originally proposed 12. These findings need to be confirmed in a validation study in symptomatic infants.

Disclosure of interest: CRK Shire, Nestle, Nutricia, MJ. SS Deca, IMS, Danone, Menarini, Nestlé. YV Abbott, Aspen, Biocodex, Danone, Nestle, MJ, Rontis, UP. The other authors have no potential conflicts of interest to declare.

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Prolonged minimal enteral nutrition versus slowly advancing enteral nutrition in very low birth weight infants: Randomized controlled trial

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Objectives and Study: Preterm infants, particularly those ≤ 1250 grams birth weight are at increased risk of developing feeding intolerance and necrotizing enterocolitis. The benefits of early initiation and daily increments of enteral feeds on early achievement of full enteral feeding in preterm infants have been shown in many studies. But the data on enteral feeding of extremely low birth weight infants is limited. The aim of the study was to determine the effect of two different feeding strategies on the incidence of feeding intolerance and time to achieve full enteral feeding in preterm infants with birth weight ≤ 1250 grams and gestational age ≤ 32 weeks.

Methods: Prospective randomized controlled trial comparing the effects of prolonged minimal enteral nutrition (MEN) with slowly advancing enteral nutrition. Incidence of feeding intolerance and time to reach full enteral feeding sustained for 72 hours were defined as primary outcomes. Infants were randomly allocated to one of the two feeding strategies designated as group 1: prolonged MEN or group 2: slowly advancing enteral nutrition. In both groups feeding was started within the first 48 hours with 10-15 ml/kg/d. In group 1 feed volume was not increased for 5 days, whereas in group 2 feed volumes were advanced by 20-25 ml/kg/d until 150 ml/kg/d feed volume was achieved.

Results: Feeding intolerance, time to achieve full enteral feeding, sepsis, duration of hospitalization and mortality were similar between the groups. Daily weight gain (19.2 vs 15.9; p < 0.001) and weight at discharge (2280 vs 2075; p = 0.01) were significantly higher in prolonged MEN group. Incidence of necrotizing enterocolitis was 5% in slowly advancing feeding group, whereas no case of necrotizing enterocolitis was observed in prolonged MEN group (p = 0.024).

Conclusion: Prolonging MEN in preterm infants with ≤ 1250 grams birth weight has not been associated with a delay in time to achieve full enteral feeding and prolonged duration of hospitalization. It may provide an advantage over slowly advancing enteral nutrition in terms of avoiding necrotizing enterocolitis development and improving daily weight gain.

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Pre- and postnatal nutrient restriction has differential effects on systemic immunity development in preterm piglets

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Objectives and Study: Preterm infants (born at < 37 weeks of gestation) have increased risk of developing life-threatening infections in the neonatal period. A large fraction of preterm infants suffer from prenatal nutrient restriction, resulting in intrauterine growth retardation and low birth weight. After birth, all preterm infants fed mother’s own milk or human donor milk do not receive sufficient nutrients to achieve growth rates similar to those in utero. Using preterm pigs as a model for preterm infants, we investigated how pre- and postnatal nutrient restriction affects the development of systemic immune parameters.

Method: Preterm pigs (n=78), born by caesarian section at 90% gestation, received gradually increasing amounts of enteral nutrition with bovine milk, with or without nutrient fortification, using dietary protein supplements. This resulted in groups of pigs fed lower protein (LOW, 27g/L, n=21) and higher protein levels (CON, 55g/L, n=57). Within the CON group, we identified pigs with low birth weight (LBW, lower 25th percentile, BW=606g, Std. Error=89g, n=13) and normal birth weight (NBW, middle 50th percentile BW=886g, Std. Error=99g, n=26). Blood samples were collected at birth, day 8 and day 19 to evaluate systemic immune endpoints. Blood leucocyte counts were analyzed using an automated cell counter. Lymphocytes were differentiated into subsets, including T-cells (CD3+), helper T-cells (CD3+CD4+CD8-, TH), cytotoxic T-cells (CD3+CD4-CD8+, TC) and memory T-cells (CD3+CD4+CD8+, TM), by flow cytometry. Blood neutrophil phagocytosis function was tested by ex vivo stimulation with Escherichia coli followed by flow cytometry analysis.

Results: The lower birthweight of LBW pigs (-32%, p<0.001) was associated with lower postnatal growth rate (-38%, p<LT; 0.01), otherwise they did not differ from NBW pigs in haematological parameters or neutrophil function, neither at birth, day 8 nor day 19. Across the postnatal pigs, LOW pigs showed reduced growth rate until day 19 (-56% relative to CON pigs, p<LT; 0.001). On day 8, LOW pigs had more TH (+81%, p<LT; 0.001), TC (+116%, p<LT; 0.001) and TM (+192%, p<LT; 0.01) cells, relative to CON. The elevated TH number persisted until day 19 (+32%, p<LT; 0.05), but monocyte numbers were reduced at this time, relative to CON (-47%, p<LT; 0.05). Neutrophil phagocytosis function did not differ between the groups, neither on day 8 nor 19.

Conclusion: During the first weeks of life in preterm pigs, prenatal nutrient restriction did not affect systemic immune development, while postnatal nutrient restriction modulated systemic T-cell responses. Our results indicate that intrauterine growth restricted preterm infants, if fed adequately, will develop their systemic immune system similarly to that in normal-weight preterm infants. However, postnatal nutrient restriction may modulate the systemic Th1/Th2 balance, and thereby influence the susceptibility to systemic infections in preterm neonates.

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Nutrient fortification improves postnatal growth without effects on neurodevelopment in preterm pigs

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Objectives and Study: Relatively high nutrient and energy intakes are recommended in preterm infants to achieve a postnatal growth rate similar to corresponding intrauterine growth rates. These recommendations are based on studies associating poor postnatal growth with negative long-term outcomes, including poor neurodevelopment. Recommended amounts of nutrients, especially protein, cannot be met alone by feeding mother's own milk or donor human milk. Nutrient fortification of human milk is therefore required to support growth and development in preterm infants. Conversely, excessive enteral nutrient intake may induce gut dysfunction and feeding intolerance. Using preterm pigs as a model, we investigated if nutrient fortification with bovine colostrum, which contains high levels of proteins and bioactive components, could improve growth, organ development and brain function within the first three weeks after preterm birth.

Method: Preterm pigs (90% gestation, n = 31) from two sows were block randomized into two groups. In a blinded setting, they were fed increasing enteral volumes (32-180 mL/kg/d) of bovine milk (CONT, n = 16) or bovine milk fortified with colostrum (FORT, n = 15) for 19 d. Protein intakes were 3-5 g/kg/d in CONT and 3-10 g/kg/d in FORT groups respectively. Cognitive function was assessed in a spatial T-maze system, testing memory and learning at 13-18 d. At 19 d, blood biochemistry values and weights of all internal organs were recorded to assess how nutrient fortification affected body and organ development.

Results: Preterm pigs receiving the FORT diet grew faster than CONT pigs (32 vs. 19 g/kg/d, P<0.01, Figure), thus preventing extra-uterine growth restriction. Improved growth was accompanied with increased levels of creatinine kinase, phosphate and aspartate aminotransferase and decreased level of iron (all P<0.05). Among organs, the FORT diet increased stomach, intestine, colon, liver, spleen, kidney and heart weights (20-60%, all P<0.05) at 19 d. Expressed relative to body weight (g/kg), intestinal length and weight, liver and spleen were affected (10-50% gain, P<0.05). The FORT diet tended to increase absolute weights of some brain regions (cerebellum, cerebrum, brain stem, P<0.15), but relative brain weight was lower in FORT vs. CONT pigs (19 vs. 23 g/kg, P<0.01). Memory and learning were identical between the FORT and CONT preterm pigs, as tested in a spatial T-maze test showing identical group performances in two different settings, a basic and reverse test phase (see Figure).

Conclusion: Growth restriction during the first 3 weeks after preterm birth was prevented by nutrient fortification with a tendency to improved brain growth but without changes in functional neurodevelopmental outcomes in pigs. This indicates pronounced brain sparing effects in nutrient-restricted preterm neonates, at least short-term. Conversely, fortification had marked effects on liver and spleen growth, potentially stimulating metabolic and immune development. Long-term effects of nutrient fortification in early life remain to be better investigated to balance the risk and benefits of high nutrient intake and rapid growth in preterm infants.
Growth

Body weight (g)

Day

T-maze

Correct choices (%)

Acquisition

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[Growth and cognition performance in control and nutrient-fortified preterm pigs]
Presence of 6'SL during lactation promotes attention, learning/memory and reduces impulsivity in the adult offspring in mice

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Objective: Human Milk Oligosaccharides (HMOs) represent the third most abundant component of breast milk and are thought to play a role in brain development. Supplementation during lactation with sialyllated HMOs increases brain ganglioside content, improves cognition and reduces anxiety in rodents. However, the understanding of both the long-term programming effect of early life exposure to HMOs and the mechanisms of action by which they act is still incomplete. In this study, we investigate the short- and long-term neuro-behavioural effects of rearing by a sialyl-transferase gene 1 (St6Gal1) knock-out mouse, which exhibit an absence of 6’sialyllactose (6'SL) from its milk.

Method: We use a cross-fostering design, between St6Gal1 knock-out and wild-type mice, to dissociate effects mediated by absence of 6'SL from the milk and by the deletion of St6Gal1 in the pups. We evaluate the adult offspring in a battery of behavioural tasks measuring attention, learning & memory and impulsivity.

Results: Absence of 6'SL from milk resulted in adult offspring exhibiting: (1) a deficit of prepulse inhibition, (2) delayed acquisition of the compound discrimination in the attention set shifting task, (3) reduced retention memory in the Barnes maze, (4) reduced performance in the object recognition, (5) reduced spontaneous alteration in the T-maze and (6) increased home-cage locomotor activity. Deletion of St6Gal1 gene only resulted in: (1) delayed acquisition of the compound discrimination in the attention set shifting task, (2) a deficit in novel object recognition memory and (3) reduced spontaneous alternation in the T-maze. All these effects were observed in the absence of growth or neurodevelopmental alterations (assessed using the Fox scale).

Conclusions: This study suggests that early-life dietary 6'SL plays a key role in the programming of attentional processing, learning and possibly impulsivity. The most likely mediator of these effects may be gut microbiota; through either metabolites of 6'SL or alteration of the microbiota composition itself due to the differential impact of 6'SL on specific bacterial population(s). In conclusion, our findings bring another piece of evidence that sialyllated HMOs play a key role in supporting brain development and early programming of associated adult brain functions. This study supports the concept that early-life presence in the diet of HMOs, specifically 6'SL, may benefit neurodevelopment and improves associated adult brain functions, such as attention, learning/memory and possibly reduce impulsivity.

Disclosure of interest: While conducting this study, Jonas Hauser and Pascal Steiner were employed by Nestlé SA.

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Objectives and Study: Early life nutrition plays an important role in regulate the metabolism in later life. Neuregulin 4 (Nrg4), mainly expressed in brown adipose tissue (BAT), specially activate EGF receptor-ErbB4 to attenuate de novo lipogenesis (DNL) in hepatocytes. The present study aimed to evaluate the effects of postnatal overfeeding and fatty dietary on Nrg4 regulation and hepatic lipogenesis.

Method: 1. Male Sprague-Dawley rat pup litters were adjusted to litter sizes of three (small litters, SL) or ten (normal litters, NL) on postnatal day 3. After weaning (P21), the NLs were given standard chow and high fat diet (NL-HF), while the SLs were given standard chow, fish oil diet enriched with polyunsaturated fatty acids (SL-FO) and high fat diet (SL-HF) until postnatal week 13 (W13). 2. Human pre-adipocytes (HPA) cells were treated by eicosapentaenoic acid (EPA) with or without PPARγ antagonist during the differentiation. 3. HepG2 cells were induced by sodium oleate (OA) and then stimulated by recombinant Nrg4 protein for 48h. 4. Nrg4 was measured by ELISA kit. The mRNA and protein expression in tissue and cells were determined by real-time qPCR and Western-blot. The triglyceride (TG) content of liver and cells were determined by TG assay kits.

Results: 1. Postnatal overfeeding increase body weight and hepatic TG accumulation and gene expression of hepatic DNL enzymes (ACC, SCD1, FASN and SREBP-1c) and reduced Nrg4 expression in BAT and SAT; 2. Compared standard dietary, fish oil dietary reduced weight gain and hepatic disorders, increased Nrg4 expression in BAT and SAT (P<0.05); high-fat dietary in SL aggravated hepatic disorders (P<LT; 0.05) and did not change Nrg4 expression in BAT and SAT. 3. During HPA differentiation, EPA treatment increased Nrg4 mRNA expression and PPARγ antagonist suppressed the mRNA expression in HPA as well as the Nrg4 level in cell culture supernatants. 4. In vitro, TG content and the DNL related genes were increased by OA(p<LT; 0.05), which were reversed by the treatment of recombinant Nrg4 protein in HepG2 cells with ErbB4 overexpression (p<LT; 0.05).

Conclusion: Overfeeding related to small-litter rearing during lactation contributes to the NAFLD phenotype, possibly through down-regulated Nrg4 in BAT and upregulated DNL in liver. Fish oil diets reversed the changes of Nrg4 and improve postnatal overfed outcomes in adulthood.

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Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study

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Objectives and Study: Rodent studies demonstrate that supplementing the maternal diet with choline during pregnancy produces life-long cognitive benefits for the offspring. In contrast, the two experimental studies examining cognitive effects of maternal choline supplementation in humans produced inconsistent results, perhaps because of poor participant adherence and/or uncontrolled variation in intake of choline or other nutrients. We examined the effects of maternal choline supplementation during pregnancy on infant cognition, with intake of choline and other nutrients tightly controlled.

Method: Women entering their third trimester were randomized to consume, until delivery, either 480 mg choline/d (n = 13) or 930mg choline/d (n = 13). Infant information processing speed and visuospatial memory were tested at 4, 7, 10, and 13mo of age (n = 24).

Results: Mean reaction time (RT) averaged across the four ages was significantly faster or infants born to mothers in the 930 (vs. 480) mg choline/d group. Furthermore, for the 480-mg choline/d group, there was a significant linear effect of exposure duration (infants exposed longer showed faster RTs).

Conclusion: This result indicates that maternal consumption of approximately twice the recommended amount of choline during the last trimester improves infant information processing speed. The linear exposure duration effect suggests that even modest increases in maternal choline intake during pregnancy may produce cognitive benefits for offspring.

Disclosure of interest: The research of this submission was funded by: The egg nutrition center; The beef checkoff; Cornell University related and USDA related grants. Authors other declarations: Caudill, Strupp & Canfield - Some research funds from Balchem Canfield - A one-time consulting fee from Nestle None of the funding sources had any role in trial design; participant recruitment; data collection, analysis and interpretation; manuscript preparation; or any aspect pertinent to the study.
The Prevention of Obesity in Toddlers (PROBIT) trial

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Objectives and Study: The PROBIT trial (clinicaltrials.gov registration number: NCT03131284) aimed to decrease the prevalence of overweight/obesity at two years of life, in a group of toddlers whose parents were provided with an intensive standardized educational intervention from their child’s birth onwards (intervention arm), compared to a group of toddlers whose parents were not provided with any additional intervention besides the usual care and follow-up provided by their paediatrician (control arm).

Methods: The target population of the trial consisted of healthy newborns from Verona, Italy, whose parents or guardians accepted to participate in the study at the time of the first newborn well visit, by informed consent. Parents were assigned to the control or intervention group according to which group their paediatrician was randomly assigned to. In the intervention arm, parents were provided, at the well visits of the first two years of the newborn’s life, with oral and written information on behaviours to adopt for their child to be protected from obesity: breast feeding, feeding on demand, responsive feeding, correct time of introduction of complementary feeding, portions shaped on the child’s appetite, avoiding added sugar and beverages other than milk and water, practicing active game with the child, alternating protein sources correctly and avoiding protein excess. All the information and the tips were resumed in 12 A5 size sheets to be inserted in the regional follow-up loose-leaf notebook all parents are provided with, at the time of the neonatal well visit. The “control paediatricians” were just asked to provide the newborns’ parents with usual care and follow-up according to the well visits calendar. Overweight and obesity at two years of age were defined as a BMI above the 85th and the 95th percentile according to the CDC growth charts, respectively. Overweight at one year of age was defined as a BMI above the 85th percentile according to the WHO growth charts. Rates of overweight/obesity and average BMI were compared across the two arms by Chi Squared test and ANOVA respectively. Moreover, a binary logistic model and a general linear model were run, with overweight/obesity or BMI as dependent variables, and arm, parental BMI and parental socio-economic status as independent variables, respectively.

Results: Twenty-two paediatricians (eleven for arm) recruited 469 newborns overall, of whom only one dropped-out from the intervention arm. Two hundreds and sixteen “control” children were compared to 252 “intervention” children. At two year of age, the groups did not differ significantly in the percentage of overweight or obesity and in the average BMI (all p > 0.05). Among children from at least one obese parent (24 control vs 29 intervention subjects), the control group had a significant higher prevalence of obesity at two years of age, compared with the intervention group (12% vs 0%, p = 0.03).

Conclusion: The PROBIT trial was not effective in decreasing the prevalence of obesity at two years of age in the general population. However, it highlighted that an early educational intervention could be effective in infants with obese parents, suggesting. If confirmed, this result will support strategies of obesity prevention based on selective intervention in at risk infants.

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Resting energy expenditure in children with cerebral palsy: accuracy of prediction formulae and elaboration of a population specific formula

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Objectives and Study: Energy requirements are difficult to predict in children with cerebral palsy (CP). Resting energy expenditure (REE), necessary for personalized nutritional intervention is most commonly estimated using prediction formulae because indirect calorimetry (IC), despite being the reference method, is not affordable in all Nutrition Units. Aim of the present study is to evaluate the accuracy of the most commonly used REE prediction formulae compared to REE measured with IC in children with CP. The secondary aim is to elaborate a new population specific predictive formula for estimation of REE in children with CP.

Method: Children and adolescents with spastic quadriplegic cerebral palsy (SQCP) aged 6-18 years (n=54) underwent nutritional assessment (feeding history, anthropometry, triceps skinfold thickness measurement), estimation of REE with the five most commonly used predictive formulae (World Health Organization (WHO) formula, Harris-Benedict formula, Schofield formula based on weight and Schofield formula based on weight and height and the Oxford Formula), and measurement of REE with IC.

Results: The mean difference (standard deviation, SD) between the estimated and measured REE was 64 (238) kcal/day for the WHO formula, 79 (226) kcal/day for the Schofield based on weight formula, 79 (223) kcal/day for Schofield based on weight and height formula, 55 (226) kcal/day for the Oxford formula, 37 (224) kcal/day for the Harris-Benedict formula, 0 (213) kcal/day for the newly elaborated population specific formula. Considering the large SD of the bias shown by all formulae, none of them can be reliably applied at the individual level due to under and over-estimation of REE. Figure 1 shows the presence of negative proportional bias for all formulae including the population-specific formula.
Conclusion: All commonly used REE predictive formulas are inaccurate at the population and individual level making them inappropriate for estimation of REE in children with SQCP and posing patients at risk of under or over-feeding. The newly elaborated population-specific formula, despite being accurate at the population level, does not perform better than the traditional REE formulae at the individual level.

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NOURRITURE - Nutrition neonatale et nutrition de l’enfant

N-O-029

Dairy lipids incorporation in the diet increased Omega-3 status in post-weaning rats.

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Objectives and Study: The status of docosahexaenoic acid (DHA, C22:6n-3) is essential for neurocognitive and visual development in children. As the conversion pathway from α-linolenic acid (ALA, C18:3n-3) to DHA is very low, the direct supplementation of preformed DHA might be required to increase its brain status. In most infant formulas, the lipid part is composed of a blend of vegetable oils (VO). The partial reintroduction of dairy lipids (DL) in these formulas could be beneficial to stimulate the Omega-3 fatty acid conversion pathway. In summary, recent studies have shown that the brain DHA status was higher when rodents were fed DL diets than VO diets in specific conditions: i) with an Omega-6/Omega-3 ratio of 5 against 10, and 2.3% of ALA against 1.3% of ALA, respectively[ChaB1]; ii) with the same ratio and the same ALA quantity in rats previously depleted in ALA. However, the mechanism involved remains unclear (lipid matrix effect, ratio effect, ALA quantity effect).

The purpose of this study is to evaluate the effect of DL on Omega-3 metabolism in rats after weaning with the same 2.3% ALA in diets and the same ratio of Omega-6/Omega-3 of 5.

Method: 4 groups of Sprague Dawley male rats (64 animals) were fed during 6 weeks after weaning, with a 10% fat lipid diet, whose the lipid portion contained VO alone or a half-half mixture of DL and VO[ChaB1], supplemented or not with 0.5% of DHA. All diets contained 2.3% ALA with an Omega-6/Omega-3 ratio of 5, in accordance with nutritional recommendations in France.

The total fatty acid composition of 5 tissues and brain phospholipids was evaluated by gas chromatography mass spectrometry. Activity and expression of desaturase enzymes and plasma parameters (total and free cholesterol, HDL, triglycerides) were studied. Groups were compared with a linear mixed model, followed by a Tukey-Kramer post-hoc test (fdr adjustment) and by redundancy analysis (RDA).

Results: Compared to the VO diet, the partial introduction of DL increased the proportion of DHA in brain phospholipids, in retina and heart. In the brain and retina, the DHA status reached the same level than groups directly supplemented with DHA. DL diet led to an increase in n-3 docosapentaenoic acid (DPA, C22:5n-3) and n-3 eicosapentaenoic acid (EPA, 20:5 n-3) in the heart, liver and red blood cells. Especially in the heart, DPA was the only fatty acids, which increased in both DL diets compare to VO diets.

DL diets increased n-3 and n-6 precursors ALA and linoleic acid in liver and adipose tissue, and the proportion of DL diet specific fatty acids, as myristic acid and short and medium-chain fatty acids (≤C12 carbons). DL intake in the diet increased cholesterol level compared to the VO group, without changing the total cholesterol / HDL ratio.

Conclusion: Incorporation of DL in the diet improved: 1) the status of DHA in brain and retina at the same levels than animals directly supplemented with DHA; 2) the DPA content in the other tissues (liver, heart, red blood cells).

We suppose that short and medium-chain fatty acids could prevent precursors ALA from mitochondrial β-oxidation, and that myristic acid from the DL diets could increase conversion from ALA to DHA, DPA and EPA.

Disclosure of interest: This work received financial support from Lactalis Group (France). Baudry C. and Le Ruyet P. are employed by Lactalis group.

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Maternal high-fat diet exposure leads to persistent inflammation and altered metabolism of liver of male offspring

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Objectives and Study: Increasing evidence suggests a potential link between perinatal nutrient environment and metabolic outcome in offspring. The liver is considered as a target organ responsible for metabolic reprogramming, particularly related to overnutrition. Here we investigated whether high-fat diet (HFD) intake during critical period contributes to hepatic dysregulation and glucose metabolism in male offspring at weaning and early adulthood.

Method: Female C57BL/6J mice were fed a high-fat diet (HFD; 53.8% fat by calories) or normal chow (NC) for 4weeks before mating and continued through pregnancy and lactation. Female mice were mated with age-matched male chow-fed mice. At postnatal day 21, male offspring mice were sacrificed for blood and liver analysis. For long-term studies, offspring from either HFD- or NC-fed mother were weaned on normal chow diet. At 10 weeks old, a 2-hr hyperinsulinaemic-euglycaemic clamp was conducted in awake mice to assess insulin sensitivity (n=5~7/group). After the clamp, mice were sacrificed then liver, gastrocnemius, and brown adipose tissue were collected. The mRNA expression of liver was determined by real-time polymerase chain reaction (RT-qPCR).

Results: Male offspring from HFD-fed mother (Off-HFD mother; n=11-16) and NC-fed mother (Off-NC mother; n=26-32) showed similar body weights at postnatal day 7, 21, and 70. Interestingly, at postnatal day 21, Off-HFD mother showed significant increases in fat mass (pLT; 0.0001) as well as fasting plasma glucose (p=0.01), insulin (p=0.005) and cholesterol (p=0.018) levels compared to Off-NC mother. RT-qPCR analysis showed that liver mRNA levels of IL-6, MCP-1, IL-1B, and F4/80 were significantly increased by 2-5 fold in Off-HFD mother, indicating highly inflammatory state of liver. Compared to Off-NC mother, hepatic expression of gluconeogenic genes, G6Pase and PEPCK, were elevated by 5-fold in Off-HFD mother (pLT; 0.05), which is consistent with their hyperglycaemia. Hepatic expression of GLUT4, IRS-1, and PDK4 as well as lipid metabolic genes, CD36, SREBP1c, and SCD1 were increased, whereas hepatic CPT1a mRNA level was reduced by~60% in Off-HFD mother. At 10 weeks of age, persistent hepatic inflammation and increased expression of lipid and glucose uptake genes (CD36, GLUT4) were observed in Off-HFD mother as compared to Off-NC mother. Despite similar body weight and fasting plasma glucose, Off-HFD mother developed insulin resistance with impaired insulin action in liver during the insulin clamp. As a result, insulin-stimulated glucose metabolism in both skeletal muscle and brown adipose tissue were reduced by 30~50% in Off-HFD mother as compared to Off-NC mother.

Conclusion: Our findings demonstrate that maternal exposure to high-fat feeding causes obesity and type 2 diabetes phenotypes partly due to inflammation and altered hepatic metabolism in male offspring.

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Glucocorticoids overexposure induced by neonatal overfeeding enhanced hepatic lipogenesis

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Objectives and Study: Postnatal overfed could active tissue glucocorticoids (GC) activity by up-regulation 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and increase sensitive to high-fat(HF) diet induced Non-alcoholic fatty liver disease (NAFLD). The present study aimed to evaluate the effects of postnatal overfeeding on GC regulation and lipogenesis in liver and to observe the impact of GC on hepatocyte lipid metabolism.

Method: Male Sprague-Dawley rat pup litters were adjusted to litter sizes of three (small litters, SL) or ten (normal litters, NL) on postnatal day 3 and then given standard chow from postnatal week 3 (W3) to W13. In vitro, HepG2 cells were stimulated by GC, Sodium oleate (OA), mifepristone separately or combined together. Intracellular lipid droplets, TG concentrations and gene expression of GC and lipid metabolism were measured in hepatic tissue or HepG2 cells.

Results: The body and liver weight gain and concentrations of TG in liver were significantly increased in SL compared to NL rats at W3 and W13 (P<0.05), as well as mRNA expression of hepatic 11β-HSD1, acetyl-CoA carboxylase 1 (ACC), stearoyl-CoA desaturase-1 (SCD1), fatty acid synthase (FASN) and their nuclear transcription factor - sterol regulatory element binding protein-1c (SREBP-1c) (P<0.05). In vitro, intracellular lipid droplets and TG content in HepG2 cells were increased under stimulation with GC (P<0.05) and OA and more significance when GC and OA together (P<0.05), as well as the expression of ACC, FASN, SCD1 and SREBP-1c (P<0.05). All above action was disappeared when glucocorticoids receptor (GR) was blocked by mifepristone.

Conclusion: Postnatal overfeeding induced GC overexposure through 11β-HSD1 up-regulation in liver. GC activated hepatic DNL by GR and led to hepatic lipid accumulation, which increased NAFLD occurrence in adulthood of postnatal overfed rat.

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Newly developed infant gut simulator model for human milk oligosaccharide fermentation

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Objectives and Study: During infancy, the infant gut microbiota is unstable and undergoes dynamic developmental changes. It affects important host functions such as growth and maturation of the intestine and early immune programming. Human milk oligosaccharides (HMOs), a structurally diverse group of carbohydrates from human breast milk, shape the evolving infant gut microbiota by serving as a fermentable energy source. We developed an infant colon fermentation model to examine the effect of 2'-fucossyllactose (2'-FL) on the composition of the microbiota and production of microbial metabolites. A medium without added carbohydrates, galacto-oligosaccharides (GOS) and lactose were used as controls.

Methods: EnteroMIX® colon simulator model with four sequentially connected vessels represented different parts of the colon. Nine parallel simulations were performed to investigate how 2'-FL, lactose and GOS affected the infant microbiota composition and metabolites during the 48 hours simulations. From the faecal donors, five were breast-fed and four were mostly formula-fed with age variation from 0.5 to 8 months. Total bifidobacteria were quantified by real-time qPCR and overall microbial composition was analyzed by 16S rRNA amplicon sequencing. Microbial metabolites were analyzed by chromatographic methods.

Results: There was an increased variation among the simulations due to multiple donors. 2'-FL as well as GOS and lactose increased the amount of total bifidobacteria, but no differences were found between feeding types of the donors when simulations were combined. The predominant taxa detected by sequencing were Bifidobacterium, Lactobacillus, Enterobacteriaceae and Veillonella. Alpha-diversity was lower in simulations with breast-fed donors compared to formula-fed donors, and beta-diversity clustering showed significant effects of donor, feeding type, and carbohydrate on microbiota composition. The concentrations of short chain fatty acids and lactic acid were highest in the lactose and GOS simulations and lowest in control simulations; being intermediate in the 2'-FL simulations indicating gentler fermentation. The levels of branched chain fatty acids and biogenic amines were similar among control, 2'-FL, GOS and lactose; however, samples from breast-fed donors produced more ethylamine than those from formula-fed donors.

Conclusion: We validated the EnteroMIX® colon simulator using infant faecal inocula as a method for modelling the effect of carbohydrates on infant microbiota composition and metabolism. As individual variation of the gut microbiota composition is high in infancy, the effect of formula and breast-feeding were masked with low sample size, and selecting more narrow age range for faecal sample donors could decrease variation. The impact of 2'-FL on the microbiota was closer to the control suggesting milder fermentation that might be more suitable for the immature infant gut. This simulator model is a good tool to get data relevant for humans instead of using animal models.

Disclosure of interest: The work was funded by DuPont Nutrition and Health. Krista Salli, Johanna Hirvonen, Ashley Hibberd, Markku Saarinen, Heli Putaala, Kirsti Tiilhonen, Johanna Maukonen, and Arthur Ouwehand are employees of DuPont, which manufactures and sells 2'-fucossyllactose. The authors declare no other conflict of interest regarding this study.

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Dietary treatment with extensively hydrolyzed casein formula with the probiotic L.rhamnosus GG prevents the occurrence of functional gastrointestinal disorders in children with cow’s milk allergy

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Objectives and Study: Cow's milk allergy (CMA) could be a risk factor for the development of functional gastrointestinal disorders (FGIDs) in children. We aimed to investigate whether the addition of the probiotic L.rhamnosus GG (LGG) to the extensively hydrolyzed casein formula (EHCF) for the CMA treatment could reduce the occurrence of FGIDs.

Method: The study population was enrolled from a cohort of children with a positive history for CMA in the first year of life, treated with EHCF alone or in combination with LGG, and evidence of oral tolerance acquisition to cow’s milk proteins (CMP) from at least 12 months. These children were re-evaluated by pediatricians blinded to the previous treatment. Anamnestic, demographic and clinical data (including sociodemographic features, parental history of FGIDs, environmental tobacco smoke exposure, number of siblings, and pet ownership) were collected from all enrolled children. The investigators involved in the study performed a full clinical evaluation in all study subjects. The diagnosis of FGIDs (vomiting and aerophagia, abdominal pain, constipation and incontinence) was performed in all cases according to the Rome III diagnostic criteria (QPGS-RIII).

Results: A total of 220 subjects were included in the study (130 male, aged from 4 to 6 yrs), 110 in EHCF+LGG and 110 in EHCF group. All children were from families of middle socioeconomic status and lived in urban areas. Main features of the study groups were similar. The rate of subjects with at least ≥1 FGID in the EHCF+LGG group was significantly lower compared to EHCF group (40% vs 16.4%, pLT; 0.05). In addition, a significant difference between the EHCF+LGG and the EHCF group was observed for diagnosis of vomiting and aerophagia (17.3% vs 8.2%, pLT; 0.05), or abdominal pain (18.2% vs 9.1%, pLT; 0.05), or constipation and incontinence (21.8% vs 10%, pLT; 0.05).

Conclusion: The study performed in a well-characterized population of children with previous diagnosis of CMA, shows that EHCF+LGG is superior to EHCF for the prevention of FGIDs. Further studies are needed to elucidate the mechanisms of this beneficial effect.

Disclosure of interest: The study was supported at least in part by an unrestricted grant from Mead Johnson Nutrition (USA) devolved to Department of Translational Medical Science, University of Naples “Federico II” Naples, Italy.
Milk fat globule membrane alone and in combination with a prebiotic moderates the impact of maternal separation on behavior and gut microbiota

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Objectives and Study: Maternal separation (MS) of rat pups is a robust model of early-life stress that highlights the impact of stressful episodes during development. This stress induces long-term alterations to behavior and brain neurochemistry. We previously reported that milk fat globule membrane (Lacprodan MFGM-10®, 15 g/kg) and a polydextrose / galactooligosaccharide (7 g/kg each) prebiotic blend, respectively, or in combination attenuated MS-induced visceral pain hypersensitivity and ameliorated impaired spatial learning. From the same animal study, we further explored whether the protective effects of the dietary intervention, simultaneously modulate expressions of genes known to be correlated with the gut-brain stress axis, and if it mediates changes in gut microbiota.

Method: The MS protocol was conducted as described in O'Mahony et al., 2009 (rats separated from their mothers for 3 h /day from postnatal day (PND) 2 to 12). Starting at weaning (PND 21), both non-separated (NS) and MS offspring were provided with or without supplementation of MFGM, prebiotic blend or a combination of both. Spatial memory, visceral sensitivity and stress reactivity were assessed in adulthood. Gene transcripts associated with cognition and stress were measured in the prefrontal cortex and the caecal microbiota composition was analysed.

Results: MS rats demonstrated visceral hypersensitivity to colorectal distension which was ameliorated by MFGM and the combination of MFGM+prebiotic. Furthermore, MS rats showed impairments in spatial and reference memory in the Morris water maze. Cognitive performance in this test was improved by the prebiotic blend, MFGM alone, as well as the combination. Coinciding with these observations, corticosterone was higher in MS rats following the acute stress and this response was reduced by prebiotic and the combination, suggesting moderation of stress reactivity. Interestingly, the combination of MFGM and prebiotic reduced the impact of early life stress on the mineralocorticoid receptor (MR) expression as well as myelin associated glycoprotein (MAG) in the frontal cortex. Moreover, MFGM and prebiotic supplementation alone, and in combination, induced changes in microbiome composition at the Phylum, Family and Genus level. In addition, MFGM and prebiotic supplementation alone, and in combination, had a significant effect on beta diversity; with a more profound effect in MS animals compared to NS animals.

Conclusion: The changes to MR and MAG expressions upon feeding MFGM and prebiotic to MS rats indicate that regulation of the gut brain stress axis as well as altered myelination patterns may be involved in the previously reported amelioration of visceral hypersensitivity, cognitive impairment, and exaggerated stress response in MS rats. Given that the impact of MS on the gut microbiota and behaviour was lessened by MFGM and prebiotics, this dietary supplementation may offer a solution to early-life stress induced alterations in the microbiota-gut-brain axis.

Disclosure of interest: R.V. Waworuntu, S.I Manurung, and B.M Berg are employees of Mead Johnson Nutrition S. OMahony,K-A McVey Neufeld, M. M. Pusceddu,K. Murphy,C.R. Strain, C. Stanton, T.G. Dinan, and J.F. Cryan declare no conflict of interest Financial support was obtained from Science Foundation Ireland and Mead Johnson Nutrition.

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Refeeding with lactose and milk minerals alters the gut microbiota and expands plasma volume in a piglet model of moderate malnutrition

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Objectives and Study: Moderate malnutrition includes stunted growth, wasting and disturbed electrolyte profile. The small intestine is atrophic and patients often present symptoms of gut dysbiosis and diarrhea. Refeeding of patients with moderate malnutrition is mostly based on corn-soy blends with added sucrose. It is however unclear if other sugars like lactose, or a combination of lactose and milk minerals can show superior effects with regard to growth, clinical and paraclinical endpoints and endpoints related to gut mucosal function and gut microbiota.

Method: Four-week old pigs were fed a pure low-protein maize diet for 17 days to induce symptoms of moderate malnutrition. Tissues were collected from a subsample of pigs at this stage to represent pigs with moderate malnutrition (MAL, n=7) whereas the rest were fed a corn-soy blend until day 42, with added sucrose (SUC, n=11), lactose (LAC, n=11) or whey permeate (a dairy product high in lactose and milk minerals, PERM, n=11). All three products were added at 10% of the total diet.

Results: Malnutrition was characterized by slow growth and low P, albumin and bilirubin, while Na, K, alanine aminotransferase and gammaglutamyl transferase were increased (all P< 0.05). Following refeeding, growth, body composition and organ weights were similar for all groups. Relative to baseline before malnutrition, MAL pigs showed decreased in vitro TNF-α response to TLR2 agonist (immune paralysis), and refeeding recovered the immune response to similar levels among the three refeeding groups (all P< 0.05). Refeeding was further associated with a marked reduction in creatine kinase and alkaline phosphatase in the three refeeding groups relative to MAL, whereas creatinine was decreased and albumin increased only in SUC and LAC (all P< 0.05). Refeeding was also associated with higher plasma Mg, P and K (P< 0.05) relative to MAL. Relative to SUC and LAC there was a lowering in PERM of both Ca, Mg, Fe, albumin, hematocrit, erythrocytes and hemoglobin (all P< 0.05), suggesting an expansion of plasma volume in PERM. This was also associated with an increased urine creatinine concentration in PERM versus LAC (tendency) and SUC (P< 0.05), indicating lower urine production. Likewise, the concentration of Na, K, Cl and protein were numerically elevated in PERM versus LAC and SUC indicating of more concentrated urine. The brush border enzyme activity were largely similar for MAL, LAC, PERM and SUC. The gut microbiota (GM), in MAL and SUC showed differences (P< 0.05) in α- and β-diversity as compared to LAC and PERM in samples collected from rectal region. Furthermore, between LAC/PERM and MAL or SUC, significant differences (adjusted P< 0.05) in the prevalence of more than 30 bacterial species (many of them typically know as beneficial members) belonging to Bacteroidales, Lactobacillales, Clostridiales and Proteobacteria were determined.

Conclusion: Refeeding after moderate malnutrition with a corn-soy based diet with added permeate, induces altered gut microbiome, expands plasma volume and reduces urine production relative to diets enriched with sucrose or lactose. In patients with normal cardiac function but low blood pressure, expansion of plasma volume can be regarded as a benefit to support perfusion of peripheral tissues.
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Objectives and Study: There is interest in the use of hand grip strength (GS) as an index of functional capacity, a proxy of lean mass and nutrition risk and a predictor of clinical outcomes. This study aimed to develop GS centiles in a reference population of healthy children and explore their usability in a large cohort of paediatric inpatients.

Method: 701 sick children and 536 healthy children were included. GS centiles were developed for the healthy children using the GAMLSS function in R. GS Z scores were calculated and differences between groups were explored. Associations between GS and body composition, nutrition risk and length of hospital stay were studied. ROC analysis was used to define the optimal threshold to screen nutrition risk (Paediatric Yorkhill Malnutrition Score - PYMS).

Results: Two centile charts for each gender were developed; one based on age and another for height. On average (SD), sick children had a lower GS than healthy children [age charts; 0.0 (1) vs -0.75 (1.1); p<0.0001] [height charts; -0.07 (1.1) vs -0.74 (1.2); p<0.0001]. Fat Free Mass/height\(^2\) (p<0.0001) but not Fat Mass/height\(^2\) was the strongest predictor of GS for the healthy and sick children, explaining 5-10% of measurement variation. Children at high PYMS nutrition risk (n=110) had lower GS than low risk children (mean group difference; age charts -0.43, p=0.013; height charts -0.51, p<0.0001). GS was not predictive of length of hospital stay. There was an inverse moderate correlation between GS and CRP (age charts: r=-0.23, p<0.0001; height charts: r=-0.23, p<0.0001). For age charts, a GS threshold of -0.85 SD had sensitivity, specificity, positive and negative predictive values of 66%, 60%, 29% and 88%. For the height charts, a GS of -0.65 SD had sensitivity, specificity, positive and negative predictive values of 72%, 47%, 25% and 87%.

Conclusion: We developed paediatric GS centile charts which allow calculation of Z scores. Fat free mass but not fat mass is predictive of GS. Disease severity, as indicated by CRP, may confound this association in sick children. The performance of GS to screen for nutrition risk was modest.

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Objective and Study: Obesity is a serious health concern worldwide. The obesity epidemic is not of genetic origin per se, but due to unfavorable changes in lifestyle and environment. Epigenetics is defined as the heritable changes affect gene function without modifying the DNA sequence through DNA methylation and histone modifications. Epigenetic mechanisms being claimed by many to clarify the links between breastfeeding and long-term outcomes regarding obesity, the literature supporting such claims are remarkably limited. Adiponectin plays a key role in the regulation of the body energy homeostasis. It exerts positive health effects through the decrease of pro-inflammatory cytokines, enhancement of insulin sensitivity, and increase in fatty acid metabolism. The hypermethylation of the adiponectin gene promoter suppresses its expression. The present study aimed to study the adiponectin gene methylation status in breast versus formula-fed six-month-old cohort of infants.

Material and methods: The study was carried on 50 infants (25 exclusively breastfed and 25 artificially fed) aged 6-month-old. All infants enrolled in the study were subjected to full history taking, thorough clinical examination stressing on anthropometric measurement. Peripheral blood samples were taken for genetic analysis to study the methylation status of adiponectin gene promoter by methylation-specific polymerase chain reaction (MS-PCR) at 383 nt at 74 nt loci.

Results: There was a statistically significant difference between the two groups according to adiponectin gene methylation status as breastfed group showed lower methylation levels compared to formula-fed infants. In breastfeeding group 72% and 80% were unmethylated at 383 nt and 74 nt loci compared to 36% and 48% in formula feeding group respectively, that is adiponectin level was higher in breastfed infants.

Conclusions: Adiponectin gene is unmethylated in breastfed infants compared to formula-fed infants. Subsequently, adiponectin gene expression and serum levels which are protective for obesity, later on, is higher in breastfeeding.

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Safety of a modified, low protein infant formula in term infants; an RCT with a reference breast-fed group

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Objectives and Study: Conflicting evidence of protein intake and its effects on weight gain and body composition has led to an increased interest in protein quantity and quality of infant formulas. This study aimed to determine the safety of an infant formula with a modified amino acid profile and a lower protein (mLP) content on growth and body composition compared to standard protein (SP) infant formula.

Method: Term infants (aged ≤45 days) received mLP (1.7 g protein/100 kcal) or SP formula (2.1 g protein/100 kcal) until 6 months of age in a double blinded RCT. A breast-fed group (n=67) served as reference. Complementary feeding was allowed from the age of 4 months onwards. Anthropometry and body composition (measured by Air Displacement Plethysmography) was determined at baseline, 4 and 6 months of age. Blood urea nitrogen (BUN) was measured at the age of 4 months. Dietary intakes were evaluated using deuterium analysis, food questionnaires and the amount of used study formula. Primary outcome was daily weight gain from enrolment to age 4 months (non-inferiority margin: -3.0 g/day). Groups were compared using linear regression analysis and linear mixed model analysis.

Results: We randomized 178 formula-fed and enrolled 67 breast-fed infants. There were no statistically significant differences in ingested volumes between the formula groups during the intervention period, based on all three, independent methods. Weight gain (g/day) from baseline to 17 weeks was non-inferior among infants in the mLP (n=77) compared to the SP (n=76) formula group (mLP minus SP 95%CI: -0.86 [-2.68 - 0.95] g/day). Adjustment for potential confounders did not change our results. We found no differences in other growth parameters and adverse events up to 6 months of age (Table). BUN was significantly lower in the mLP formula group compared to the SP formula group.

Conclusion: An infant formula with a modified amino acid composition and 1.7 g protein/100 kcal appears to be safe and supports adequate growth and body composition during the first 6 months of life. The lower BUN in the mLP formula group despite similar intakes and comparable growth may indicate that protein metabolism is more efficient in infants fed mLP formula. Longer-term effects on BMI, body composition, and metabolic-endocrine parameters will be evaluated.
**Disclosure of interest:** Eline van der Beek is a full time employee of Nutricia Research, the R&D organization of Danone Nutricia Early Life Nutrition. Johannes van Goudoever holds patents on amino acid composition of this specific infant formula. The remaining authors declare no conflict of interest.

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Can weight equations help us to avoid weighing neurologically impaired children and adolescents?

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Objectives and Study: Weight measurements of neurologically impaired (NI) children can be cumbersome. The recently published Children’s European Estimator of Weight (CEEW) provides a reliable alternative to weight acquisition in sick children (1-18 years), based on mid upper arm circumference (MUAC), age and sex. This study aimed to assess the precision of CEEW for weight prediction (weight_{CEEW}) in predicting actual weight (weight_{TRUE}) of NI children.

Method: Prospective, cross-sectional study recruiting NI children (2 - 18 years) in 9 specialized Flemish centres. Weight for age (WFA) and MUAC z-scores were calculated based on Flemish growth charts. Mean prediction errors and 95% limits of agreement of Bland-Altman plots (of weight_{TRUE} - weight_{CEEW}) were calculated using R version 3.1.2. A p-value < 0.05 was considered statistically significant.

Results: A total of 286 (60.8% male) NI children were included at t1, with a median (Q1; Q3) age of 11.3 (7.8; 14.3) years; 17.1% had Gross Motor Function Classification (GMFCS) 1, 29.7% GMFCS2, 14.7% GMFCS3, 16.4% GMFCS4 and 22.0% GMFCS5. WFA and MUAC z scores were significantly (p&LT; 0.001) different across GMFCS classifications, with the lowest scores found in GMFCS5 (median (Q1;Q3) WFA and MUAC respectively -0.37 (-1.2;0.52) and 0.23 (-0.36;1.00) in GMFCS1 and -2.65 (-3.97;-1.33) and -0.54 (-1.42;0.25) in GMFCS5. The ratio between weight_{TRUE} and weight_{CEEW} was significantly different among GMFCS groups (p&LT; 0.001), but not between sexes (p=0.362); there was no significant correlation with age (r=-0.03 (95% CI -0.15;0.08), p=0.573). There was a strong correlation between weight_{CEEW} and weight_{TRUE} (r=0.94 (95% CI 0.92;0.95), p&LT; 0.001) overall and in each GMFCS group (r ranging from 0.93 to 0.97). The overall mean prediction error (95% CI) was -4.8 kg (-5.5;-4.1) with a lower limit of agreement (LOA) of -16.3 kg and upper LOA of 6.8 kg. The mean prediction error increased in magnitude from -1.1 (95% CI -2.4;0.31) in GMFCS1 to -7.6 (95% CI -9.6;-5.6) in GMFCS5. The number of children with a maximum prediction error of 5% was significantly different across GMFCS (36.7% GMFCS1, 25.9% GMFCS2, 0% GMFCS3, 8.5% GMFCS4, 6.3% GMFCS5; p&LT; 0.001). A relative weight prediction error of max 10% was found for 65.3% children in GMFCS1, 47.1% in GMFCS2, 19.0% in GMFCS3, 19.1% in GMFCS4 and 17.5% in GMFCS5; p&LT; 0.001.

Conclusion: The CEEW equation was highly correlated, but tends to overestimate the actual weight in neurologically impaired children, especially in those with the most severe disability. On the other hand, weight estimation errors above 10% were present also in one-third of the children in GMFCS1 and more than half of the children in GMFCS2. Future research should focus on finding a correction factor specific for each GMFCS classification.

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Glucose concentration is associated with increased efficacy of oral rehydration solution in an in vitro model of rotavirus gastroenteritis in human intestinal cells

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Objectives and Study: Oral administration of rehydration solution (ORS) is the key treatment of acute gastroenteritis in children, as it restores the impaired electrolyte balance by stimulating the intestinal sodium/glucose transporter SGLT1 and inducing fluid absorption. The major barriers toward oral rehydration is its availability in villages in developing countries, the lack of knowledge of efficacy and palatability. The chemical composition of Standard universal WHO/UNICEF solution been formulated many years ago based on fecal ion losses in cholera and is largely used in children with acute diarrhea in developing countries. In developed countries the composition of ORS is that recommended by ESPGHAN with a reduced Na content compared to the former. However different formulations are available whose content is variable within the ranges of solutes recommended by either WHO or by ESPGHAN. The main agent of acute gastroenteritis worldwide is RV. A single universal ORS would promote its use. Our aim was to evaluate the effects of different commercially available ORSs on ion transepithelial fluxes in an in-vitro model of Rotavirus (RV) diarrhea in human enterocytes.

Method: Intestinal Caco-2 cells were infected with RV SA11-strain and transepithelial ion transport was studied in Ussing chambers. Five commercially available ORSs with sodium concentration ranging from 76 to 111mmol/l glucose concentration were tested in basal standard conditions in Ringer's solution, and in RV-infected cells.

Results: None of the ORSs affected ion transport in basal condition. WHO/UNICEF ORS was more potent than standard ESPGHAN solution is enhancing ion absorption. However, in RV-infected cells, all ORSs reduced chloride secretion in comparison with standard Ringer's solution. The magnitude of the absorptive effect was highest in ORSs with high glucose concentrations (-143%; p&LT; .001) and RV-induced chloride secretion was reversed into a pro-absorptive effect. ORSs containing low glucose concentrations reduced RV-induced chloride secretion without pro-absorptive effect (-98%; p&LT; .001). No effects were found when zinc or prebiotics were added to selected ORS.

Conclusion: All ORSs inhibited RV-induced ion secretion but their efficacy was related to chemical composition. High glucose concentrations promote ion absorption suggesting the existence of a glucose cut-off concentration above which the sodium/glucose transporter activity is enhanced. Considering the limited spreading of cholera even in developing countries, the composition of ORS should be re-considered.

Disclosure of interest: The study was supported by Milte Italia.

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Vitamin D regulates the expression of milk-derived miRNAs in mammary epithelial cells

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Objectives and Study: Mammary epithelial cells produce mammary fluid in the resting gland and milk during lactation. Those cells release miRNAs in culture and in vivo. We have identified that several of the highly expressed miRNA in breast milk are known as beneficial miRNA related to immune system development and disease prevention such as mir148a-3p, mir-99a and mir-375. The regulation of miRNA secretion in milk is not clearly understood. Nutrients may be able to regulate gene and miRNA expression. Genes and nutrients seem, therefore, to interact in mutual relationship. Our aim was to investigate the effect of vitamin D and prolactin and oxytocin on the expression and release of miRNA in breast epithelial cells.

Method: Normal breast epithelial cells (MCF10A) were treated with or without 1,25(OH)2D (10⁻⁶M) for 24h. Based on our previous results of profile expression of miRNAs in milk, selected milk related miRNAs expression was assessed by RT-PCR. To study the effect of vitamin D on the secretion of miRNAs, exosomes were isolated from the culture medium of MCF10A cells treated by vitamin D, prolactin (100ng/ml) and oxytocin (35 µM).

Results: MiRNA-148 expression was upregulated by 2 folds and miRNA-99a expression by 4 fold in MCF10A cells incubated with oxytocin. MiRNA-148 expression was upregulated by 5 folds and miRNA-99a expression by 4 fold in MCF10A cells incubated with prolactin. More importantly, in MCF10A cells treated with vitamin D (10⁻⁶M) the expression of miRNA-148a, 375 and 99a was significantly up regulated in these cells. MiRNA-148 expression was upregulated by 2 folds, miRNA-375 by 4 folds and miRNA-99a expression by 5 fold. In addition miRNA-148 expression was upregulated by 2 fold and miRNA-99a by 5 fold in exosomes isolated from the culture medium of MCF10A cells following treatment with vitamin D.

Conclusion: We showed a new mechanism of regulation of miRNA expression in breast epithelial cells by vitamin D. This observation can be significant to reinforce previous studies that demonstrate the importance of nutrients in epigenetics changes. Moreover, it will enhance supplementation of vitamin D in breastfeeding mothers based on its upregulation of expression of beneficial miRNAs in milk and to supplement mammalian with vitamin D to increase the amount of beneficial miRNAs in their breast milk.

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Modulation of epigenetic mechanisms by dietary intervention in children with cow milk allergy

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Objectives and Study: Epigenetic mechanisms drive cow’s milk allergy (CMA) disease course. We aimed to investigate the effect of two dietary approaches recommended for IgE-mediated CMA treatment on these mechanisms.

Method: Randomized controlled trial on naive challenge-proved IgE-mediated CMA children assigned to two groups of dietary intervention: 1. extensively hydrolyzed casein formula with the probiotic *L. rhamnosus* GG (EHCF+LGG); or 2. soy formula (SF). At the first evaluation (T0), and after 6 (T6) and 12 months (T12) of dietary treatment a peripheral blood sample was collected for serological and epigenetic analyses. After 12 months of treatment a oral food challenge was performed to verify immune tolerance acquisition. We assessed serum concentration of IL-4, IL-5, IL-10, IFN-γ and methylation analysis of respective genes, on DNA extracted from peripheral blood CD4⁺ T cells by High Resolution Melting Real Time PCR. FoxP3 Treg-Specific-Demethylation-Region (TSDR) demethylation analysis and its expression were assessed on DNA and RNA, respectively. For miRNAs expression analysis, RNA was extracted from same cells and used for relative quantification by RT-PCR.

Results: 20 children (10 male, aged 6-12 months) were enrolled, 10 per group. Baseline demographic and clinical characteristics, DNA methylation profiles and serum levels of IL4, IL-5, IL-10, IFN-γ, FoxP3 TSDR demethylation, miRNAs expression were similar in the two study groups. At T6 and T12 a faster and stronger modulation in DNA methylation rate of IL4, IL-5, IL-10, IFN-γ, FoxP3 TSDR was observed in children treated with EHCF+LGG. DNA methylation rates significantly correlates with the respective serum levels or FoxP3 expression. Whereas, at T6 and at T12 a significant higher expression of miR- 155 and miR-146a was observed in in children treated with EHCF+LGG. At T12, we also observed a significant down-regulation of miR-21, only in children treated with EHCF+LGG. At T12, 6 out of 10 and 2 out of 10 patients acquired immune tolerance in EHCF+LGG and SF group, respectively.

Conclusion: Dietary treatment with EHCF+LGG induces a more pronounced epigenetic effect on Th1/Th2 response. Dietary influence on epigenetic mechanisms might represent an innovative approach to target the development of immune tolerance.

Disclosure of interest: The study was supported in part by the Italian Ministry of Health Grant PE-2011-02348447, and by unrestricted grant from Mead Johnson Nutrition (Evansville, Indiana, USA) devolved to CEINGE-Advanced Biotechnologies, University of Naples “Federico II” Naples, Italy.

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Butyrate exert beneficial effects on necrotizing enterocolitis in neonatal rat model

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Objectives and Study: Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease mainly affects premature infants. Although it is suggested that excessive production and accumulation of short chain fatty acids in premature infants may cause NEC, in this study we are trying to identify the role and underlying mechanisms of butyrate on NEC.

Method: Sixty-two newborn Sprague-Dawley rats were randomly divided into three experimental groups: Control group, NEC group, NEC+50mM sodium butyrate group (formula supplemented with 50mM sodium butyrate). The general state, body weight and survival time were recorded. Terminal ilea were obtained for histological and biochemical analysis. NEC was graded based on the severity of the injury from the mucosal to serosal surface. Flow cytometry were used to assess the inflammatory and immune cells. Immunostaining, Western blot and RT-PCR were performed.

Results: The activity and body weight of rats in NEC group apparently decreased compared with controls, showing abdominal distension and diarrhea with yellow green grume and bloody stool. However, pups pretreated with butyrate showed improved body activity and symptoms. Furthermore, butyrate supplementation reduced the incidence of NEC from 85% to 20%, and increased the survival rate from 30% to 90%. Rats in NEC group showed severe intestinal injury demonstrated by gross necropsy and histologic examination compared with controls. However, pretreatment with butyrate diminished the degree of injury. Immunostaining and western blot showed that the expressions of ki67, c-myc, E-cadherin and Occludin were increased in rats pretreated with butyrate compared with rats in NEC group. Furthermore, butyrate treatment substantially inhibited the mRNA and protein expressions of TLR4, MyD88, NF-κB, ER-stress and Chop in the intestine, accompanied with decreased inflammatory factors such as IL-6, IL-10 and TNF-α.

Conclusion: Taken together, these findings indicate that enteral butyrate supplementation protect against NEC by promoting intestinal regeneration and inhibiting inflammation and ER-stress.

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Objectives and Study: Malabsorption and micronutrients deficiencies characterize classical “late diagnosed” coeliac disease (CD). The literature lacks studies on the status of micronutrients among coeliac cases identified during mass screening. This study aimed to identify the prevalence of vitamin and mineral deficiencies among children with “early diagnosed” screening-identified CD in comparison to healthy controls. We also sought to determine if there is a correlation between micronutrient level among coeliac patients and TTG-IgA titer or degree of villous atrophy.

Methods: A population-based, cross-sectional, case-control study was conducted on patients with screening-identified CD diagnosed during a mass screening study [2014 to 2016 ] (100 patients, 79 females, mean age 11.4 ± 2.7 years) and compared to age, gender, and nutritionally-matched healthy controls (100 children, 81 females, mean age 10.8 ± 2.5 years). The controls were randomly selected from those who were negative for CD serological screening. Hemoglobin, serum levels of iron, ferritin, folate, vitamin B12, vitamin A, vitamin E, 25-OH vitamin D, zinc, and selenium were measured in both groups.

Results: Mean hemoglobin and serum iron level were significantly lower in CD patients as compared to healthy controls [Hemoglobin 12.56 ± 1.5 gm/dl versus 13.07 ± 0.97 gm/dl (P= 0.024); Iron 10.61 ± 5.68 µmol/L versus 13 ± 4.52 µmol/L (P =0.009), respectively]. The serum levels of vitamins and trace elements were similar between the 2 groups. There was significant negative correlation between levels of hemoglobin (Pearson's correlation coefficient -0.182, P-value = 0.021), iron (correlation coefficient -0.252, P-value = 0.001), and ferritin (correlation coefficient -0.20, P-value = 0.010) at diagnosis and serum TTG-IgA titer. There was significant positive correlation between level of hemoglobin (P-value = 0.033), iron (P-value = 0.006), and ferritin (P-value = 0.001) at diagnosis and the degree of villous atrophy. Twelve percent of the Coeliac cases had Marsh grade IIIc, 45% had Marsh grade IIIa - IIIb, and 44% had Marsh grade I-II.

Conclusion: Iron deficiency is the earliest micronutrient deficiency to develop in screening-identified coeliac cases; the level of serum iron was correlated with the TTG-IgA titer and degree of villous atrophy. The similarity of serum level of vitamins and trace elements among the coeliac cases and healthy controls could be attributed to the possibility that screening for CD offers opportunity to detect CD at an early stage before micronutrient deficiencies develop which is supported by our data that shows that minority of the screening-identified coeliac cases (12%) had severe villous atrophy.

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A third of paediatric home enterally tube fed patients receive low energy feeding regimens: results of a UK survey

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Objectives and Study: Around 16,000 paediatric patients receive home enteral tube feeding (HETF) in the UK. It has been suggested that some paediatric patients have lower energy requirements than predicted, due to clinical condition, body composition and/or low activity levels. The use of low energy tube feeding regimens (LETFR) (sole source of nutrition that provides less energy than age specific estimated energy requirements), in these patients is common; however there is currently limited guidance1 on this practice and little published literature. A survey of paediatric HETF patients was undertaken to: i) estimate the percentage of paediatric HETF patients receiving a LETFR and; ii) characterise these patients and their tube feeding regimens.

Method: In a cross-sectional survey, Dietitians from 9 UK HETF services (n=700) provided: i) an estimate of the percentage of paediatric patients on a LETFR (based on dietetic judgement) as a sole source of nutrition and; ii) for a subset of patients on a LETFR (n=103, 55% male, age 8y (SD4.6, range 1-17y) a standardised questionnaire on patient demographics (primary diagnosis, reason for tube feeding, tube type, residential status, activity level, weight and height) and feeding regimen details (energy provision, reason for LETFR, age commenced on LETFR) was completed. Estimated energy requirements were calculated using SACN EAR2 for the less active.

Results: Dietitians estimated 28% (n=196/700) of their paediatric HETF population were receiving a LETFR. In 103 paediatric patients receiving a LETFR, the most common primary diagnosis was neurological impairment (including cerebral palsy (33%) and brain injury (19%)). Patients were predominantly PEG fed (71%) due to an unsafe swallow (75%); with most (86%) residing in the family home and requiring full assistance (66%). Mean weight was 25.4kg (SD12.1, range 7-57kg), mean height 109.0cm (SD22.6, range 64-167cm)); 53% of the group had a weight < 25th centile and 76% a height < 25th centile. Overall the group were receiving 54% of the EAR/day; 1-3y 319-900kcal, 4-6y 360-1050kcal, 7-10y 434-1500kcal, 11-14y 467-1365kcal, 15-17y 500-1740kcal. Most (85%) were on a LETFR due to low energy needs, either due to being small for their age (26%), or another reason (74%), such as inactivity or mechanical ventilation. A small proportion (15%) were on a LETFR due to being unable to tolerate larger volumes of feed. Of those with low energy needs, 32% were on bespoke regimens using multiple feeds. For the majority of patients (56%) the Dietitian reported difficulty in meeting the patient's complete nutritional needs with the LETFR.

Conclusion: This is the first survey to characterise the paediatric LETFR patient group in the UK, demonstrating the high prevalence of the use of LETFR in paediatrics (up to 30%) and the complexity of managing this patient population with currently available feeds. Further research is required to assess the energy requirements of such patients in order to make recommendations for their optimal dietetic management.

References:
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Complications in Children With Neurological Impairment. 2017

Disclosure of interest: Rose Harriet Evill, conflict with Nutricia Ltd.; Joanna Berry, Harriet Mary Marjoram, Elizabeth Colyer, Lucy Stark, Emma Liesl Silbernagl, Charlie Bigwood, Sophie Chidlow, Emma Brackley, Amanda Widdows, Victoria Fisher, Samantha Armstrong and Alexa Robinson none declared; Gary Paul Hubbard, conflict with Nutricia Ltd.; Rebecca Joanne Stratton, conflict with Nutricia Ltd.
**NUTRITION - Clinical nutrition**

N-eP-007

**Growth of infants and young children born small for gestational age: growth restriction accompanied by overweight**

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**Objectives and Study:** Children born small for gestational age have increased risks of growth retardation in childhood as well as higher rates for metabolic diseases in later life. Alterations of developmental programming in SGA children lead to specific growth trajectories. We aimed to compare growth profiles of children born SGA with those born AGA, and to document an expected growth pattern for SGAs in early childhood.

**Method:** A community-based longitudinal study covering 23871 SGA children was conducted in Shanghai, China. Data were collected at 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 60 months of age (+30 days). The checkup included assessments of weight, height and head circumference. Z-score was used to assess the growth and development. BMI was used to categorize overweight or obesity. T-test was used to evaluate the difference between SGAs and AGAs. Spearman correlation coefficient was used in correlation analysis between overweight at different ages.

**Results:** At the age of 5, weight, height and head circumference of SGAs were 0.38SD, 0.67SD and 0.69SD lower compared with normal controls respectively, in average. The median BMI of SGA children was higher than that of AGAs in 4-18 months after birth. The proportion of overweight and obesity of SGAs in 4-18 months after birth was significantly higher, with an average of 16.0% for boys and 14.8% for girls. There was no correlation between overweight at 5 years and overweight before 2 years old in SGA children (p>0.05).

**Conclusion:** Children born SGA remained shorter and lighter with smaller head circumference at 5 years old. The catch-up growth of SGAs was unbalanced. 4-18 months after birth was the period of high incidence of overweight and obesity among SGA children. Overweight and obesity in SGA boys were more serious compared with SGA girls. No correlations was found between overweight at 5 years old and overweight in the first two years after birth. Growth charts for SGA children were conducted based on our data.
The nutritional status and recognition of nutritional red flag warning signs in a cohort of Flemish children with cerebral palsy

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Objectives and Study: Children with cerebral palsy (CP) are at risk for under-nutrition. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines identified objective nutritional red flag warning signs for neurologically impaired children: weight for age (WFA) &LT; -2 SD, triceps skinfold (TSF) or arm muscle area (AMA) &LT; 10th centile or faltering weight. This study aimed to 1) evaluate the nutritional status of Flemish children with CP using different anthropometric indicators; 2) assess how many children with CP had nutritional red flags according to recent ESPGHAN guidelines and whether the presence of these red flags improved at follow up; 3) identify risk factors for malnutrition.

Method: Prospective, longitudinal study recruiting children and adolescents with CP (2 - 20 years) in 9 specialized Flemish centres. Measurements were performed at baseline (t1), 6 (t2, total n=185) and 12 months (t3, total n=181). WFA z-scores were based on Flemish growth charts; TSF, subscapular skinfolds (SScSF) and AMA compared with US reference data. WFA and MUAC z-score < -2 were found in respectively 71.4% and 16.9% of the GFMCS5 children. Fat stores decreased significantly (p< 0.001) with increasing GFMCS: median TSF z-score in GFMCS1 was 0.13, for GFMCS2 0.39, GFMCS3 0.06, GFMCS4 -0.17 and GFMCS5 -0.51; median SScSF z-score in GFMCS1 was 0.33, GFMCS2 0.60, GFMCS3 0.41, GFMCS4 0.28 and GFMCS5 -0.22. Low (z-scores < -2 SD) TSF and SScSF were found in respectively 16.4% and 4.2% of the GFMCS5 children. A total of 198 (35% female) children with CP were included for follow-up; 12.7% were GFMCS1, 28.6% GFMCS2, 14.8% GFMCS3, 20.1% GFMCS4 and 23.8% GFMCS5. At t1, 85 (45.0%) had ≥1 red flag, 79/185 (42.7%) at t2 and 75/181 (41.4%) at t3. Red flags were associated with GFMCS≥3 (OR 2.75; 1.49-5.05), gastrostomy (OR 4.49; 1.19-16.9), dysphagia (OR 4.58; 2.17-9.64) and anti-epileptic drugs (OR 2.19; 1.20-4.01) at t1 (consistent findings at t2 and t3). In children with red flags at t1, 62.5% children lost weight at t2 and 53.2% at t3.

Conclusion: Children with a GFMCS classification ≥3 were at highest risk for a severe weight deficit and low subcutaneous fat stores. Half of the Flemish children with CP had at least one nutritional red flag warning sign, which were not successfully addressed in clinical practice. Children with CP presenting with dysphagia and/or receiving anti-epileptic treatment need more attention in nutritional assessment.
Efficacy and safety of lipid-lowering therapy in children with familial hypercholesterolemia

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Objectives and Study: Familial hypercholesterolemia (FH) is associated with higher risk of cardiovascular disease since childhood. HF screening in children could reduce this risk by starting lipid-lowering drugs in childhood. Our aim was to assess the efficacy and the tolerance of lipid-lowering therapy in clinical practice. A secondary objective was to evaluate the development of early atherosclerosis.

Method: We performed a retrospective study including 49 children &LT; 18 years with FH out of 110 children referred to our centre between 2006 and 2016. HF was defined by a familial history of lipid-lowering treatment for one parent or a premature cardiovascular event (&LT; 65 years in female and &LT; 55 years in male), and total cholesterol (TC) > 3 g/L and/or LDL cholesterol (LDL-C) > 2.2 or > 1.9 g/L prior or after dietary management. Vascular dysfunction was measured by ultrasound (carotid intima media thickness and flow mediated dilatation).

Results: The median age at diagnosis was 8.1 years (2.8-14.7). At diagnosis, mean TC was 3.23 ± 0.42 g/L, and mean LDL-C was 2.48 ± 0.44 g/L. 38 patients received lipid-lowering therapy (77.5%) including 36 (94.7%) with statins and 2 (5.3%) by ezetimibe alone. In 11 children, treatment was started before the age of 8 years, outside the guidelines, mainly because of severe family history of early coronary heart disease. At month 6 after treatment initiation, LDL-C was reduced by 35% (2.51 ± 0.45 vs 1.49 ± 0.34 g/L, p< 0.01). Ezetimibe was added in 11 patients and combotherapy resulted in a significantly greater mean reduction of LDL-C from baseline compared with statin monotherapy, with a supplementary decrease of LDL-C levels by 36.7% (1.8 ± 0.2 vs 1.14 ± 0.32, p=0.002). Non-invasive high-resolution ultrasound showed vascular dysfunction in 8 out of 25 patients (32%), suggesting early atherosclerosis development in FH children; half of them were overweight or obese. Lipid-lowering therapy in FH children in real life conditions, over 3 years, was safe and well tolerated. We only found a mild and transient increase of transaminases in 5 children, and a transient increase of CPK > 5 x upper limit of normal, without muscular symptoms, in 2 children.

Conclusion: Lipid-lowering therapy is effective and well tolerated in children after a 3-year follow-up. The addition of ezetimibe to statins allowed reaching therapeutic goals. Ultrasound signs of early atherosclerosis were present in 1/3 of children.

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Experience of the nutritional management of infantile onset lysosomal acid lipase deficiency (LAL-D)

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Objectives and Study: Infantile onset lysosomal acid lipase deficiency (LAL-D) is a rare inherited lysosomal storage disorder. It is a rapidly progressive condition causing cellular accumulation of cholesteryl esters and triglycerides and is characterised by gross hepatosplenomegaly, anaemia and severe malabsorption leading to growth failure and rapidly progressive liver disease. Without treatment the condition is fatal within the first year. The advent of enzyme replacement therapy (ERT) with Sebelipase alfa has transformed outcomes in this group. Alongside ERT nutritional manipulation is imperative to limit lipid substrate, manage gastrointestinal symptoms and normalise growth. Our objective is to review the nutritional management and growth outcomes in a group of infants diagnosed with LAL-D and managed with ERT over the last six years.

Methods: We report on the nutritional management and growth in 21 cases (12 male) of infantile onset LAL-D from 10 centres. Median age at diagnosis was 3 months (range 0.25 - 5.5 months). At diagnosis median growth parameter were weight for age (WFA) Z score -2.1, length for age (LFA) Z score -2.32, mid upper arm circumference (MUAC) Z score &LT; -5. At diagnosis all infants were receiving a normal fat intake with only 4 having had any dietary alteration to try address failure to thrive and / or gastrointestinal symptoms; high energy infant formula (n=1) peptide based formula (n=2), amino acid based formula (n=4) or standard total parenteral nutrition (TPN) (n=1).

Results: Following diagnosis and initiation of Sebelipase alfa treatment dietary fat intake was restricted in 19 of 21 cases. 70% (n=15) of cases initially required modified low fat TPN, 10% (n = 2) a low fat (80% MCT 20% LCT) whole protein formula, 15% (n = 3) a modular amino acid based, low fat formula and 1 case (5%) remained on an amino acid based, normal fat formula. 16 cases survive, median age 26 months (range 9.75 - 63.75 months) with significantly improved growth parameters: WFA Z score -0.1, LFA Z score -1.0, MUAC Z score 0.21. Of the 16 survivors initially requiring TPN (n = 12) 75% (n = 9) were fully established on low fat enteral feed (amino acid based n = 7, peptide based n = 1, whole protein n = 1) by 6 months of ERT treatment.

Conclusions: Although in the majority of cases some normalisation of dietary intake can be achieved all continue to need severe fat restriction. Despite general improvement in many body systems, affected by LAL-D, gastrointestinal symptoms such as vomiting, diarrhoea and bloating persist for a protracted period with only gradual improvement. Nutritional management is complex with many having ongoing gastrointestinal symptoms including oral feeding issues requiring long term tube feeding.

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NUTRITION - Nutrition and health outcomes

N-eP-011

Long-term influence of a milk fat globule membrane (MFGM)-enriched formula on language development in healthy children at 4 years old

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Objectives and Study: Nutrition in early life is one of the most important environmental factors for brain development, establishing the foundations for the development of cognitive function and language skills. Thus, nutritional deficiencies during infancy are likely to affect cognition, throughout the school years and adulthood. We aimed to analyse the long-term effects of supplemented infant formula on healthy children's language development at 4 years old. A total of 170 healthy infants between 0-2 months of age were included in a randomised double-blind study to receive either a standard infant formula (F1: n=85) or supplemented infant formula with different composition of long-chain polyunsaturated fatty acids (LC-PUFAs), milk fat globule membrane (MFGM), synbiotics, sialic acid, nucleotides and gangliosides (Nutriexpert® factor) (F2: n=85).

Method: Language development was assessed using the Oral Language Test of Navarra - Revised (PLON-R) at 4 years old. Statistical analysis: Normal distribution was assumed after using Kolmogorov-Smirnov test. PLON-R scores were compared between groups by analysis of covariance (ANCOVA) and Chi-Square test for categorical variables. The logistic regression model (Wald method) was used to calculate the odds ratios (ORs) and 95% confidence intervals (CI) for having a normal/delayed value in language development within study groups or to establish the influence of other confounder variables. Statistical analyses were performed using IBM SPSS version 22.0.

Results: At 4 years old, 89 children attended the follow-up call (F1: n=46/ F2: n=43). In adjusted analysis by sex, maternal cultural level and socioeconomic status, children fed F2 presented higher scores in use of language (p=0.012) and oral spontaneous expression (p=0.010) compared to children fed with F1. Additionally, the scores were divided in three categories: normal, need to improve and delay. Children fed F1 were classified more frequently as need to improve on use of language compared to children fed F2 (p=0.016). Finally, the regression model showed that children from F2 group have 3.5 times more probability to have better development of use of language (OR, 3.470; 95% CI, 1.436-8.386; p=0.006).

Conclusion: Early nutritional intervention with Nutriexpert® factor is associated with beneficial long-term effects in the development of child’s language at 4 years old. Further research is needed to understand the mechanisms involved in the long-term effect of this new infant formula on a better language development during childhood.

Disclosure of interest: This project has been funded by Ordesa Laboratories, S.L. Contract General Foundation of University of Granada, No.3349; Partially funded by EU Project DynaHEALTH (HORIZON 2020-GA No.633595) and SMARTFOODS (CIEN), Ministry of Industry. Spain.

Vol. 66, Supplement 2, April 2018 929
Maternal excess weight and gestational diabetes determine long-term changes in the brain structure of their offspring: an MRI study on PREOBE children at 6 years old

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Objectives and Study: Gestational diabetes (GD) and maternal excess weight are pregnancy conditions which increase the risk of future complications for both the mother and her offspring. In this study we aimed to investigate anatomical brain differences in children participants in the PREOBE-Follow up study at 6 years old due to the presence of these clinical conditions in their mothers.

Method: A total of 109 healthy children (mean age 6.02±0.14) enrolled in the PREOBE project participated in this study. They were organized in four groups, depending on their mothers' pregestational BMI and the absence/presence of GD: Group I (G-I, n=34) was formed by children born to mothers with BMI>25 who did not develop GD; Group II (G-II, n=19) included children born to mothers with BMI>25 and GD; Group III (G-III, n=44) formed by children born to normal weight mothers (18.5≤BMI<25); and, Group IV (G-IV, n=12) included children born to normal weight mothers (18.5≤BMI<25) who developed GD. All participants attended a Magnetic Resonance Imaging session in which children's BMI and an anatomical brain image were obtained. Total brain volume (TBV) of each subject was calculated. Two ANOVAs were performed to compare children BMI and TBV between groups. Brain images were used to apply a statistical method to classify called support vector machine (SVM) in order to verify the possibility of automatically recognize the individual group membership based on its anatomical brain image. This analysis was performed using PRoNTo tool v2.0. Additionally, to further investigate the effect of GD on the offspring's brain of excess weight mothers, a hierarchical clustering of the MRI data was also performed, by using Orange software.

Results: No differences were found between the 4 groups regarding children BMI or TBV at 6 years old. When we used the SVM to automatically infer whether each single subject was the offspring of a mother with or without GD, the balanced accuracy of the method was 58.09% (AUC=0.79). To further explore the effect of GD independently of BMI, we repeated the previous analysis separating normal and excess weight groups. Strong results were obtained when comparing excess weight groups G-I vs G-II (balanced accuracy=70.43%; AUC=0.76), whereas no significant results were found in the comparison between normal weight groups. The hierarchical clustering performed on excess weight groups showed one cluster formed by 79.49% of subjects from the G-I and a second one formed by 78.57% of subjects from the G-II. This result reflects that there is a strong difference between brains of children born from excess weight mothers with or without GD but a low variability inside both of these groups.

Conclusion: The study suggests that GD during pregnancy in excess weight mothers is associated with brain morphological characteristics in their offspring at 6 years old. This long-term effect has not been demonstrated in children born to normal-weight mothers with or without gestational diabetes. These results strongly support the need to new recommendations and early preventive actions in excess weight pregnant women to avoid the development of GD. Furthermore, it is necessary to develop new strategies and special protocols of care in excess weight pregnant women when they develop GD.

Disclosure of interest: *This study has been funded by the Andalusian Government, Economy, Science and Innovation Ministry (PREOBE Excellence Project Ref. P06-CTS-02341) (NCT01634464), the Spanish Ministry of Economy and Competitiveness. Ref. BFU2012-40254-C03-01 and DynaHEALTH H2020 EU Project, GA n°: 633595.
The relationship of coping, digestive symptoms and Eating-Quality-of-Life among children with oesophageal atresia: findings from the Swedish OA-QOL®-study

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Objectives and Study: Digestive morbidity and feeding difficulties may impair quality of life (QOL) in children with oesophageal atresia (OA). Additional to clinical factors, coping could explain QOL outcomes. Since no study has reported on this topic, we aimed to evaluate the relationship of coping, digestive symptoms and Eating-QOL among OA children.

Methods: Of 110 invited families of OA children 2-17 years old from Queen Silvia Children's Hospital, Gothenburg, Sweden, 103 participated (94%). Ten focus groups with 30 families generated items for a condition-specific coping questionnaire (Phase I), which was completed by a subsequent 73 families (Phase II). This study reports findings from Phase II, based on the nine questions which measured different coping strategies in "food-and-eating-situations" according to a 5-point-Likert scale. The families also answered a standardized symptom-questionnaire, and the OA-QOL©-questionnaires for children 2-7 years old (parent-report) and children 8-17 years old (child- and parent-report), which included the domain "Eating-QOL". Descriptive statistics (n, %) and Mann-Whitney-U-test (p<0.05) were used to describe and analyse the data.

Results: In "food-and-eating-situations" 56/73 (77%) of the OA children (2-17 years) used the following types of coping strategies: acceptance (93%), responsibility (89%), confronting (79%), problem-solving (79%), positive reappraisal (69%), avoidance (63%), social support seeking (54%), emotional expression (29%), distancing (23%). Among these children 26/46% reported dysphagia, 27/48% heartburn, and 16/29% vomiting problems. Eating-QOL was significantly (p<0.05) lower among children with dysphagia (both age groups), heartburn (child-report 8-17 years old), and vomiting (both age groups). Children 2-7 years old with dysphagia were reported to use coping more frequently than children without dysphagia regarding 6/9 strategies (p<0.05). OA children who used emotional expression and distancing strategies had significantly lower Eating-QOL (p<0.05, child- and parent-report), having also the lowest (median) scores on the Eating-QOL domain in both age-groups. These strategies were associated with dysphagia (p<0.05). In 8-17-year-olds, avoidance of food or food situations was related to lower Eating-QOL (Parent-report, p<0.001; Child-report p=0.001), whereas use of confrontation, was the only strategy associated to better Eating-QOL (parent-report:2-7-year-olds, p<0.0003;8-17-year-olds,p=0.016).

Conclusion: This study adds new perspective to the understanding of QOL outcomes in OA children, who develop coping strategies in early childhood. The majority of OA children experience “food-and-eating-situations” as a stressor which induce coping. OA children with dysphagia frequently use coping strategies, and coping strategies may be formed from an early age by dysphagia. Eating-QOL is associated with digestive morbidity and condition-specific coping. In follow-up care a good Eating-QOL could be supported by decreasing the morbidity and by encouraging OA children to confront their challenges rather than using disengagement coping techniques. Next we investigate a conceptual and predictive model of clinical and coping determinants on Eating-QOL.

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**Objectives and Study:** Dietary habits resembling Western style, rich in animal protein and poor in fruit and vegetables, increase the body acid load, a predictor of type 2 diabetes risk. Recently, the studies related to relationships between dietary acid load and insulin resistance has become a growing interest but there are only a few study conducted with gestational diabetes mellitus (GDM). Therefore, the aim of this study was to evaluate the potential relationship between dietary acid load in second trimester, blood lipid profiles and GDM.

**Method:** This cross-sectional study conducted with 40 women with GDM diagnosed with two-step 100g oral glucose tolerance test and 40 healthy women, aged 21-41 years, between weeks of 14-28 of pregnancy, who attended the Department of Obstetrics and Gynecology of Gulhane Training and Research Hospital. Participants with polycystic ovary syndrome, chronic diseases, pre-GDM, or multiple pregnancies were excluded. Sociodemographic information was recorded via questionnaire and anthropometrics of women were measured. Blood samples were taken after an overnight fasting. Dietary information was obtained by mean intakes of a 3-day food records (2 weekdays and 1 weekend day) and analyzed via nutrition analysis software. According to the data obtained from software analysis, animal protein (g/day) to potassium (g/day) ratio (AP/K), potential renal acid load (PRAL; mEq/day) score and net endogenous acid production (NEAP; mEq/day) were calculated from established algorithms to estimate dietary acid load. All nutrients were age and energy-adjusted before being introduced into the equation and tertiles of the scores were used for statistical analysis. ANOVA, ANCOVA, Logistic regression test were used and p value < 0.05 was considered as statistically significant. The study plan was approved by the Hospital’s Ethics Committee.

**Results:** There were no significant differences in age among tertiles of both PRAL and NEAP scores (p>0.05) while in the highest tertile of AP/K ratio were younger than those lowest tertile (p=0.031). Total energy, magnesium, folate, vitamin C, dietary fiber, carbohydrate and dietary fiber have decreased across AP/K, PRAL and NEAP scores (p&LT; 0.05). Women with highest tertile of AP/K, PRAL and NEAP scores were more likely to have fasting blood glucose and LDL-cholesterol levels compared to lowest tertile in adjusted models (p&LT; 0.05). Women in the highest tertile of AP/K and PRAL had more than 6.67 and 1.74 times increased risk of GDM, respectively (p&LT; 0.05). Women with high dietary PRAL and NEAP scores tended to consume more red meat and less vegetable, fruit (p&LT; 0.05).

**Conclusion:** In this study, we found that dietary acid load was associated with an increased risk of gestational diabetes mellitus. Recent studies have been indicated that capillary or urine pH can be altered by dietary modifications in healthy individuals. Therefore, our finding may have crucial public health implications related to dietary habits for the future. If future researches especially randomised controlled trials confirm that nutrient-induced improvements in acid-base balance is related to provide of glucose homeostasis, this may promote to prepare more specific dietary recommendations to reduce dietary acid load in both pre-gestational and gestational period.

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Objective and Study: Infant feeding practices have been extensively investigated in the context of pediatric Celiac Disease (CeD) but studies focusing on overall diets of young children following the weaning period are lacking. Overall diet may be important in the development of CeD via changes in the gut microbiome. Our aim was to examine the association between common dietary patterns in infants and the occurrence of CeD autoimmunity during childhood.

Methods: This study was embedded in the Generation R Study, and focused on 1,997 children born between April 2002 and January 2006 in Rotterdam, the Netherlands. Food consumption around 1y of age was assessed with a validated food-frequency questionnaire and used in a posteriori extraction of dietary patterns (DPs), using Principal Component Analysis (PCA) and Reduced Rank Regression (RRR). A previous a priori diet quality score for preschool children was also considered. CeD autoimmunity was evaluated at 6y and categorized as serum transglutaminase-2 autoantibody (TG2A) concentrations below and above 7 U/mL. Associations between diet adherence scores and CeD autoimmunity were examined using multivariable binary logistic regression models adjusted for sociodemographic, anthropometric and lifestyle factors of the mother and child.

Results: Higher adherence to the PCA-derived Prudent DP (vegetables, vegetable oils, pasta and grains) was significantly associated with lower odds of CeD autoimmunity (OR 0.67, 95% CI [0.54-0.84]). Adherence to the remaining a posteriori-derived DPs or to the diet quality score was not significantly associated with CeD autoimmunity.

Conclusions: Our results show that adherence to an early-life Prudent DP is associated with a lower prevalence of CeD autoimmunity. These observations suggest that dietary patterns may be involved in the development of CeD during childhood.

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Cerebrospinal fluid and plasma proteomics to discover new biomarkers for sepsis and diet interventions in preterm neonates

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Objectives and Study: Infection remains a leading cause of neonatal morbidity and mortality, particularly in preterm infants, and it is associated with neuroinflammation and brain injury. Immunomodulatory milk diets may attenuate peripheral inflammation. We hypothesized that systemic bacterial infection induces neuroinflammation in preterm neonates that is reflected by proteome changes in cerebrospinal fluid (CSF) and plasma. Using preterm pigs as a model for preterm infants, we also investigated if a bioactive milk diet, bovine colostrum, would ameliorate inflammation and infection-induced changes to CSF and plasma proteins.

Method: Immediately after birth, preterm pigs were intra-arterially administered 10⁹ CFU/kg body weight of cultured *Staphylococcus epidermidis* (SE) a pathogen frequently causing sepsis in preterm infants. Pigs were fed parenterally (SE, n=15) or enterally with bovine colostrum (SE+COL, n=14). A third non-infected group was given parenteral nutrition and served as controls (CON, n=14). After 24 h, CSF and plasma samples were subjected to untargeted proteomic analysis on a Thermo q-Trap mass spectrometer. Protein identity and abundance were determined using the MaxQuant and Perseus software, and analysed by a linear mixed-effect model with Tukey post hoc test and FDR adjustment of P values. Detected protein differences (adjusted P<0.1) were classified according to cellular functions: Neuroinflammation, brain function, transportation, complement system and metabolism.

Results: After 24 h, leukopenia, blood-brain barrier disruption and neuroinflammation were observed in SE-infected preterm pigs. Colostrum feeding reduced SE abundance ameliorated neuroinflammation and alleviated leukocyte response in blood and CSF. A total of 117 and 125 proteins with differential abundance were annotated in plasma and CSF, respectively. Neuropeptide Y, one of the most abundant peptides in the nervous system, showed lower abundance in CSF of SE vs. CON pigs, but increased in SE+COL pigs. Multiple inflammation-related proteins, including C-reactive protein, haptoglobin, LBP, CD109, Von Willebrand factor, increased in SE pigs, relative to CON, with more variable responses in SE+COL pigs. Complement proteins, including C1QC, C3 and C5, were increased in plasma and CSF of SE pigs but were lowered by colostrum feeding. ApoA4, a transcellular lipid transport modulator, was specifically increased in SE+COL pigs.

Conclusion: Systemic neonatal infection is associated with neuroinflammation and marked changes to CSF and plasma proteins, as detected by proteomics. These proteins associated with neuroinflammation and may serve as biomarkers for systemic infection in preterm neonates. Feeding an immunomodulatory milk diet may attenuate neuroinflammation but did not consistently affect the CSF and plasma biomarkers of systemic infection.

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Effect of probiotics on the gut microbiota composition of children suffering from severe acute malnutrition in Uganda

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Objectives and Study: Severe acute malnutrition (SAM) is a major challenge in low-income countries resulting in up to 1 million child deaths annually. Diarrhea is a common complication and is associated with morbidity, longer hospitalization and fatality rates often exceeding 20%. Probiotics have previously been shown to reduce incidence and duration of diarrhea in other groups of children, but the effect on diarrhea in children suffering from SAM is only sparsely investigated. The recently completed ProbiSAM-study investigated the effect on diarrhea of administering a combination of two probiotics (Lactobacillus rhamnosus GG (LGG) and Bifidobacterium animalis subsp. lactis BB-12) to children hospitalized with SAM in Uganda. Probiotic administration had no effects on days with diarrhea during in-patient treatment, but during the outpatient treatment (8-12 weeks after hospitalization) a significant 26% decrease in days with diarrhea was observed in the probiotic group (Grenov et al., 2017, JPGN, 64:396-403). In the present study we determine the gut microbiota (GM) composition of the ProbiSAM cohort to elucidate possible links between probiotic administration and GM changes in children suffering from SAM.

Method: In a double-blind study-design 400 children admitted to hospital with SAM were randomized to receiving either probiotics (daily dose 10 billion colony-forming units of LGG and BB-12, ratio 1:1) or placebo during inpatient as well 8-12 weeks of out-patient treatment. Fecal samples were collected at admission to hospital, at discharge and after 8 weeks of outpatient treatment (follow-up), as well as from 30 age-matched, healthy controls from the same community setting. DNA was extracted and GM composition determined by high-throughput 16S rRNA gene amplicon sequencing. Chr. Hansen A/S partly funded the study, but had no role in study design and data interpretation.

Results: At admission children suffering from non-oedematous SAM had a distinct GM composition compared to children suffering from oedematous SAM. During treatment the GM composition evolved, with the GM at admission, discharge and follow-up being significantly different from each other, and with a significantly higher number of observed species (pr. sample) at follow-up, compared to admission and discharge. At follow-up the GM had evolved to a composition close to that of the healthy controls. Administration of probiotics induced minor compositional differences in overall GM composition at both discharge and follow-up, but these effects were mainly driven by the presence or absence of the administered probiotics. However, for children where one or both of the 2 administered probiotic species were detected (“probiotic responders”), the number of observed species was significantly higher compared to children not administered the probiotic and probiotic non-responders at both discharge and follow-up.

Conclusion: During treatment of children suffering from SAM, pronounced GM changes happen. Administration of probiotics has significant effects on GM composition, but this is mainly driven by the presence or absence of the administered probiotics. Probiotic responders harbor a slight, but significantly, increased number of observed species compared to children not administered the probiotic and probiotic non-responders.

Disclosure of interest: The study was partly funded by Chr Hansen A/S. The company had no role in study design, data interpretation or the conclusions of the study.

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**Management of low profile balloon gastrojejunal feeding tubes in children a single centre experience**

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**Objectives and Study:** An increasing number of children require trans-pyloric feeding where gastric feeds are either not tolerated or contraindicated. A variety of devices are available for use. These may be placed radiologically, endoscopically or surgically; dependant on device used, tolerance and predicted duration of use. Complications arising from these devices or placements are well recognised.

**Aim:** To review the use of low profile balloon gastrojejunal tubes in a large tertiary children's hospital in the UK.

**Method:** Retrospective review of all children who underwent placement of a low profile balloon gastrojejunal tube (AMT G-JET®, MIC-KEY GJ Feeding Tube) over a 12 month period. Information obtained included mode of placement and complications arising from the procedure or device. Information was also obtained on changes to device or modality of feeding. Children with devices other than a low profile balloon gastrojejunal tube were excluded from the study. All children were established on trans-pyloric feeding prior to the study date.

**Results:** 53 children underwent low profile gastrojejunal tube placements for transpyloric feeding in the study period. 31 male (58%); 22 female (42%). Age range 10 months-18 years (median 4 years) 125 gastrojejunal tube placements occurred in 53 children. 113 of 14F- AMT G-JET device: 12 of 16F-MIC-KEY GJ Feeding Tube device.

79% of devices were placed under fluoroscopic guidance with 25% of children requiring sedation. The frequency of device placement ranged from 3 to 266 days (median 77 days). Complications related to placement occurred in 9 procedures (4 children) and include:
- Small bowel perforation following radiological placement
- Dislodgement of jejunal tube within 72 hours of placement

Device failure requiring replacement occurred in 51 devices (41%) in 30 children. This occurred within 3 months of initial placement in 24 devices (48%), this included dislodgement, port dysfunction, leakage, balloon rupture, blockage, device fracture and pain.
Device replacements were carried out electively at 3 month intervals following device failure or complication. The mean duration of elective device replacement was 98 days (median 84). Of the 16 children (30%) with a single device placement in 2017, the mean device longevity was 134 days (median 136) range 27-316 days. Low profile balloon gastrojejunal tubes were discontinued in a total of 10 children. 4 children reverted to nasojejunal tube feeding; 2 children, due to ongoing intestinal dysmotility, require parental nutrition and enteral nutrition was discontinued. One child had a surgical jejunostomy and 3 were successfully weaned onto gastric feeds.

**Conclusion:** Transpyloric tube feeding has resulted in a significant improvement in providing enteral feeding access for children. Regular replacements may eliminate at least 52% of device failures. The advantage of the 14F AMT device over the 16F MIC-KEY is its small size allowing for placement in smaller children. The need for frequent repeated regular replacement may have an impact on its long term use.

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**NUTRITION - Nutrition and health outcomes**

N-eP-019

**Status of metabolic syndrome in Chinese children and adolescents: Analysis from a Chinese National Study**

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**Objectives and Study:** Metabolic syndrome (MetS) has become a national epidemic in China recently but few studies have described its status in young people. The present study aims to estimate the prevalence of MetS and its components among Chinese children and adolescents and possible associations with age, gender, geographics, economic development, birth weight, and parental education.

**Method:** The data was derived from 15045 participants in an obesity intervention study during 2013-14 (7-18 years, 7711 male, 7334 female across seven Chinese provinces). Data on anthropometry, geographical location (north, south), and economic development (developed, underdeveloped), birth weight, and parental education were obtained. Blood samples were collected to measure fasting glucose (FG), triglyceride, and high-density cholesterol (HDL-C) levels. MetS was defined according to the definition by International Diabetes Federation. Logistic regression was used to assess the association between MetS and other factors.

**Results:** The MetS prevalence was 2.3%, higher in males (2.8 vs. 1.7% in females), northern regions (3.1%), developed regions (2.9%) and in older subjects (16-18 years) (all P< 0.05). Among the five classical MetS components, abdominal obesity and low HDL-C were most prevalent (21.8% and 14.4%, respectively). Elevated FG was the least prevalent component (3.0% overall). According to logistic regression, MetS did not correlate with birth weight or parental education, whereas abdominal obesity correlated with high birth weight (HBW, odds ratio 1.48) and secondary or higher parental education level, while elevated FG levels correlated negatively with HBW (odds ratio 0.49).

**Conclusion:** MetS components, especially abdominal obesity and HDL-C, were prevalent in Chinese children and adolescents, while MetS itself was less common. Moreover, children with HBW or higher parental education are on higher abdominal obesity risk, but have no correlation with MetS. Strategies designed to prevent MetS and its components are greatly needed in Chinese children and adolescents.
<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Geographic location</th>
<th>Economical development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n=15045)</td>
<td>Male (n=7711)</td>
<td>Female (n=7334)</td>
</tr>
<tr>
<td>MetS</td>
<td>2.3 (2.1,2.5)</td>
<td>2.8 (2.4,3.2)</td>
<td>1.7 (1.4,2.0)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>21.8 (21.1,22.5)</td>
<td>21.2 (20.3,22.1)</td>
<td>22.5 (21.5,23)</td>
</tr>
<tr>
<td>High BP</td>
<td>3.7 (3.4,4.0)</td>
<td>4.6 (4.1,5.1)</td>
<td>2.7 (2.3,3.1)</td>
</tr>
<tr>
<td>Low HDL-C level</td>
<td>14.4 (13.8,15.0)</td>
<td>15.8 (15.0,16.6)</td>
<td>12.9 (12.1,13.)</td>
</tr>
<tr>
<td>High triglyceride</td>
<td>5.5 (5.1,5.9)</td>
<td>5.0 (4.5,5.5)</td>
<td>6.0 (5.5,6.5)</td>
</tr>
<tr>
<td>Elevated FG level</td>
<td>3.0 (2.7,3.3)</td>
<td>4.1 (3.7,4.5)</td>
<td>1.8 (1.5,2.1)</td>
</tr>
</tbody>
</table>

[Prevalence of MetS and its components in China]

Data are percentage with 95% confidence interval. MetS, metabolic syndrome; BP, blood pressure; HDL-C, HDL cholesterol; FG, fasting glucose.

\(^a\) p< 0.05 , male vs. female, assessed by chi-square test for categorical variables. \(^b\) p< 0.05 , north vs. south, assessed by chi-square test for categorical variables. \(^c\) p< 0.05 , underdeveloped vs. developed, assessed by chi-square test for categorical variables.

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A pooled analysis of stool consistency of infants fed partially hydrolyzed whey-based or intact protein-based infant formula

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Objectives and Study: The protein sources of routine infant formulas differ by the fractions of cow’s milk protein used (whey and/or casein) and degrees of hydrolysis. Stool consistency may differ based upon the protein source of the formula consumed which can have implications for caregiver perception of tolerance. The objective of this analysis was to compare pooled data on caregiver-reported stool consistency of infants fed either an intact whey/casein-based formula (CMF) or a partially hydrolyzed 100% whey-based formula (PHF-W) from a single manufacturer.

Method: Individual subject data from seven infant growth studies (3 CMF, 4 PHF-W) were pooled and analyzed. All studies included healthy, full-term exclusively formula-fed infants enrolled at 14 days of age with outcomes assessed at baseline, 1, 2, 3, and 4 months. Stool consistency (categorized as liquid, soft, formed, or hard) was recorded by caregivers for two days prior to each study visit. Two different statistical models were utilized. In one approach, stool consistency was modeled as a multinomial outcome in the four categories separately for each time point with adjustment for clustering by study. The second approach was a repeated measures model using a binary outcome of soft versus not soft stools including a group by time interaction as well as adjustment for clustering within studies and infants; post-hoc tests at each time point compared soft or not soft stool between the two groups. In both models, alpha was adjusted for multiple comparisons. The intention to treat analysis is reported.

Results: In total, data from 511 infants were included (197 CMF, 314 PHF-W). When considering all stool consistency categories, infants fed PHF-W had a significantly higher proportion of soft and lower proportion of hard stools as compared to infants fed CMF at 1 (soft: 79% versus 49%, p=0.005; hard: 1% versus 11%, p=0.001) and 2 months (soft: 80% versus 44%, p=0.004; hard: 1% versus 4%, p=0.002). This trend continued past 2 months (3 months: soft: 78% versus 48%, p=0.039; hard: 1% versus 3%, p=0.104; 4 months: soft: 76% versus 56%, p=0.0130; hard: &LT; 1% versus 3%, p=0.018), but did not reach statistical significance based on the adjusted alpha. At 2 months of age, PHF-W-fed infants had a significantly lower proportion of formed stools compared to CMF (11% versus 42%, p=0.008). Using the repeated measures model with a binary outcome, infants fed PHF-W had a significantly higher proportion of soft stools than those fed CMF at 1, 2, 3, and 4 months (all ps≤0.003).

Conclusion: Differences in stool consistency can be seen between infants fed PHF-W and CMF with PHF-W fed infants having a higher proportion of soft stools and lower proportion of hard stools than those fed CMF. This difference could be perceived as beneficial to caregivers and influence their decision-making when choosing an infant formula.

Disclosure of interest: This abstract was sponsored by Nestle Nutrition. LC, BK, RC are employees of Nestle Nutrition.

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Plasma sphingomyelins of infants differ according to source of milk fat

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Objectives and Study: Infant formulas are typically manufactured from skimmed milk and vegetable oils. This implies the loss of milk fat globule membranes, which have been found to provide nutritionally important polar lipids, including sphingolipids. Recent research has related sphingomyelins to cognitive development and metabolic diseases with specific emphasis on the sphingomyelin species pattern. Currently little is known about the influence of dietary sphingomyelin and fatty acid composition on infant plasma sphingomyelin species. Thus, we wanted to compare in our study the effect of different dietary fatty acid patterns on infant plasma sphingomyelins and carnitine esters as markers of fatty acid oxidation.

Method: In the Australian multicentre, double blind, controlled TIGGA study healthy term infants were randomised to receive either a control infant formula (CIF) with a pure plant oil fat component or a formula with a goat milk fat/plant oil mixture (GIF) up to the age of 4 month. Exclusively breastfed infants were followed as a reference group. Plasma samples collected at the age of 4 months were analysed for sphingomyelin species and acyl-carnitines by liquid chromatography - tandem mass spectrometry. Student t-tests were performed to investigate differences between groups. Significance was accepted at a Bonferroni corrected p-value < 0.05.

Results: Twenty sphingomyelin (SM) species could be analysed in 57 GIF infants, 50 CIF infants and 37 breast fed infants. The total measured sphingomyelin concentrations were not significantly different between the formula groups, but were 15 % (CIF) and 21% (GIF) lower in the formula groups than in the breast fed group. Correspondingly most species were lower in the formula groups, and SM(32:1) and SM(39:1) were the only species found higher in a formula group (CIF) than in the breast fed group. Between the formula groups 6 species were found different. SM(32:2), SM(35:1), SM(36:2) and SM(42:1) were higher in the GIF group, while SM(32:1) and SM(38:1) were higher in the CIF group. The remaining species, including SM(34:1) and SM(42:2), which contributed most to total sphingomyelin in all groups were not different between formula groups. Total carnitine, acetyl-carnitine, and long chain C16:0 and C18:1 acyl-carnitine concentrations were not different between the groups. For the medium chain carnitine esters C12:0, C14:1, C10:1, and C8:1 higher concentrations were found in the CIF group than in the GIF group. While for the other carnitines differences were significant but modest the C8:1 carnitine ester was twice as high in the CIF group as in GIF and breast fed infants.

Conclusion: We could identify significantly different patterns of sphingomyelin species and acyl-carnitines in infants fed CIF, GIF or breast milk. However, the profiles did not directly reflect the dietary fatty acid pattern. This agrees with the previously observed hydrolysis of dietary sphingomyelin during absorption and re-acylation of sphingosine and de novo synthesis as major sphingomyelin sources. The species composition of plasma sphingomyelin seems to be influenced more by the substrate preferences of the ceramide synthases than by differences in the oxidation of fatty acids, as indicated by the carnitine ester patterns.

Disclosure of interest: Colin Prosser is an employee of a company processing goats’ milk, but this did not influence the content of the abstract. No conflicts for the other authors.

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Milk fat globule membrane as a source of gangliosides and phospholipids in infancy to support brain development and healthy growth

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Objectives and Study: Human milk is the optimal source of nutrition for infants. When breastfeeding is not possible, infant and follow-on formulas are the only suitable alternative nutrition. Historically milk fat has been replaced with vegetable oils, and therefore formulas are usually depleted of the milk fat globule membrane (MFGM). This important structure stabilizes the milk fat globules but also provides bioactive components such as complex milk lipids (CML, i.e. phospholipids and gangliosides) and MFGM proteins. An infant formula and a follow-on formula have been formulated with ingredients enriched in MFGM to provide CML at similar levels to those found in human milk. The primary objective of the CLING study was to investigate whether feeding formulas enriched in CML from MFGM up to 12 months of age improves neurodevelopmental outcome at 12 months in healthy children as compared to a control standard formula. Secondary objectives include determining if MFGM supplementation improves neurodevelopmental outcome at 6 months, as well as other measures of growth and development, immunity and gut maturation during the first year of life.

Method: The CLING study is a randomized, multi-site, double-blinded and controlled prospective clinical trial stratified for gender. Healthy full-term infants (gestational age 35-41 weeks and birth weight 2500-4000 g) born in the Fuzhou province, China and whose parents had chosen to formula-feed were recruited within 14 days postnatally and randomized to one of the two formula-fed groups. Infant formula was provided from recruitment to 6 months of age and follow-on formula was then provided until 12 months of age. Apart from the levels of MFGM components, the control and intervention formulas had identical composition. A group of infants who were exclusively breastfed for 4-6 months were recruited as the reference group. Neurodevelopmental outcomes at 6 and 12 months were measured using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Serum gangliosides and gut microbiota were measured in a subset in each group. Anthropometry, (serious) adverse events, formula tolerance, routine blood tests and immune response to vaccines were also recorded.

Results: After enrolment, infants were allocated to one of the formula-fed groups (n = 226) or were recruited into the reference group (n = 206). The dropout rates in the formula-fed groups and reference group were 22.5% and 11.6%, respectively. Breastfed and formula-fed infants had similar weight-for-age (WA) and weight-for-length (WL) z-scores at birth and at 6 months of age. Breastfed infants had significantly higher WA and WL z-scores at 42 days of age in both males and females and WA z-score in females only at 4 months of age. 355 infants attended the Bayley-III assessment at 6 months of age and 357 infants at 12 months of age. The cognitive outcomes will be presented.

Conclusion: The preliminary findings from the CLING study in healthy infants showed that supplementation of MFGM in the first 12 months of life supports adequate growth and is well tolerated.

Disclosure of interest: Gallier, S. and Rowan, A. are employees of Fonterra Co-operative Group Ltd, New Zealand. This work was supported by the New Zealand Primary Growth Partnership post-farm gate dairy programme, funded by Fonterra Co-operative Group Ltd and the New Zealand Ministry for Primary Industries.

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Objectives and Study: Phospholipids and sphingomyelin have a central role in infant nutrition, phospholipid acting as a nutrient carrier of long chain polyunsaturated fatty acids and sphingomyelin having an important role in cognitive function. The aim of the study was to develop and validate an analytical method to precisely characterize and quantify these compounds in maternal milk.

Method: Phospholipids and sphingomyelin were extracted using chloroform and methanol and separated on Polaris 3 Si column 250 × 2.0mm from Varian and analyzed by high performance liquid chromatography (HPLC) coupled with mass spectrometer detector (MS).

Results: The analytical method was validated by comparison to HPLC coupled with evaporative light scattering detector (ELSD) and $^{31}$P-NMR techniques and repeatability, intermediate reproducibility, and recovery values were calculated. The relative standard deviation of repeatability (CV(r)) and intermediate reproducibility (CV(iR)) values ranged between 2.3 and 7.2 % and 9.5 and 17.8%, respectively and the recovery values between 96 and 109%. The validated method was tested on human milk samples and on infant formula which were analysed also by HPLC coupled with ELSD. In human milk, sphingomyelin (9.28 mg100mL$^{-1}$) was the most abundant compound, followed by phosphatidylcholine (5.39 mg100mL$^{-1}$), phosphatidylethanolamine (2.85 mg100mL$^{-1}$) and phosphatidylinositol (1.82 mg100mL$^{-1}$).

Conclusion: In this study a validated HPLC-MS/MS procedure to quantify phospholipids and sphingomyelin in human milk has been established and validated. This method has the advantages of robustness for the quantification of PL classes and sphingomyelin in maternal milk and of molecular species determination comparing to the existing methods. A limitation of our method is lack of chromatographic resolution for the quantification of phosphatidylserine. The established method was applied to analyze infant formula and results compared to the ones obtained with HPLC-ELS D demonstrating the feasibility of its application to different matrices.

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Comparrison between baby led weaning and traditional spoon feeding on iron status and growth in breastfed infants

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Objectives and Study: The current guideline of World Health Organization recommends that infants are initially offered smoothly pureed foods, with subsequent introduction of semisolid and finger foods. This is known as the traditional method of spoon feeding. Over the last 10 years, an alternative method known as ‘baby-led weaning’ (BLW) has been really popular in Indonesia. With BLW, infants are allowed to self-feed family foods in their whole form instead special-prepared foods. Weaning period is a peak period for faltering in child’s growth and iron deficiencies. Infants following BLW may be at increased risk of growth faltering, based on the assumption that not all infants will have the motor skills to feed themselves the amount of food they require, and that many of the first foods offered will be low in energy and iron. The aim of this study is to compare traditional and BLW methods in the risk of iron deficiency anemia and growth faltering of breastfed infants.

Methods: A cross-sectional study was undertaken in 9 - 15 months breastfed infants admitted to Bedah Hospital Surabaya from August - October 2017. Exclusion criteria were infants suffering from chronic conditions such as cerebral palsy, congenital deformities and chromosomal disorders. Infants with urinary tract infection, hypothyroid, and tuberculosis were also excluded. Biochemical assessment of Haemoglobin (Hb), Serum Transferrin (ST) and Serum Ferritin (SF) was measured, as well anthropometry of body weight and body length. Diagnosis of iron deficiency anemia was made based on WHO criteria. Growth anthropometry was interpreted based on WHO criteria. Data were analyzed by Chi-square.

Results: Out of all infants, 12/30 were boys and 15/30 were following BLW. Mean age of the infants in this study was 12.6±2.14 months old. Mean Hb level, ST level and SF in BLW group was 10.9±0.55 g/dl, 11.6±7.13%, 19.1±18.40ug/dl prospectively, while in the traditional group were 12.5±0.75 g/dl, 24.6±7.92%, 57.6±18.78 ug/dl prospectively. Iron deficiency anemia was higher in infants who were following BLW group than in the traditional group. (13/15 vs 3/15, OR 26.000 95%CI 3.686-183.418, p < 0.001). Underweight was higher in infants who were following BLW then in the traditional group. (13/15 vs 3/15, OR 26.000 95%CI 3.686-183.418, p &LT; 0.001). Stunted were higher in infants who were following BLW (2/15 vs none, OR 1.667 95%CI 1.103-2.519. p=0.017) than in the traditional group.

Conclusion: In breastfed infants, those who were following BLW are in higher risk of iron deficiency anemia, underweight and stunted than those who were fed traditionally.

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Iron and vitamin D status at 2 years of age in healthy New Zealand and Australian children randomised to cow's milk or growing up milk

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Objectives and Study: Iron deficiency (ID) and vitamin D deficiency (VDD) are prevalent in young New Zealand (NZ) and Australian children. Low dietary intakes and a lack of policy on vitamin D supplementation or fortification remain significant factors to these deficiencies. The role of Growing Up Milks (GUM), also referred to as Follow-Up Formula for Young Children or Young Child Formula to improve nutritional status and the dietary intakes of young NZ and Australian children has not yet been explored. The aim of this study was to investigate the effect of a micronutrient fortified, reduced energy GUM (GUMLi) compared to Cow's milk (CM) consumed for one year on serum ferritin (SF) and 25-hydroxyvitamin D [25(OH)D] concentrations at 24 months of age in healthy NZ and Australian children as a secondary analysis of the Growing Up Milk - Lite (GUMLi) Trial.

Method: The GUMLi Trial was a multi-centre, double-blinded, randomised controlled trial of healthy 1-year-old NZ and Australian children conducted from 2015 to 2017. Participants were randomly assigned to receive either GUMLi (1.7 mg Fe/100 mL; 1.3 µg vitamin D/100 mL) or standard CM (0.02 mg Fe/100 mL; 0.06 µg vitamin D/100 mL) for 12 months. Adherence was measured in monthly intervals and defined as consumption of 300 ml of study milk per day on 80% of the days within the monitored interval. Blood samples were collected at baseline and following the 12-month intervention. ID was defined as serum ferritin < 12 g/L and iron deficiency anaemia (IDA) as combined SF < 12 g/L and Hb < 100 g/L, both in the absence of infection. VDD was defined as 25(OH)D < 50 nmol/L. Secondary outcomes included dietary iron and vitamin D intakes from food frequency questionnaire (FFQ) and SF and 25(OH)D concentrations at 24 months of age. All regression models have adjusted for baseline outcome and study centre.

Results: One hundred and sixty participants were randomised. Adherence to the protocol was 89% over the 12 month intervention period. GUMLi was a significant contributor to dietary iron and vitamin D at 24 months of age when compared to CM. The adjusted mean difference between the intervention and control in SF and 25(OH)D concentrations was 18.2 µg/L (95% CI: 14.2, 22.2 µg/L; p<0.0001 and 16.6 nmol/L (95% CI: 9.9, 23.3 nmol/L; p<0.0001) respectively. After 12 months of the intervention ID and IDA were found in 45% and 2% of the CM group respectively with no occurrences of either in the GUMLi group.

Conclusion: The use of GUMLi for 12 months significantly improved dietary iron and vitamin D intakes and iron and vitamin D status of healthy NZ and Australian children at 2 years of age when compared to CM.

Disclosure of interest: The authors declare that they have no competing interests. The GUMLi Trial received an investigator-initiated grant from Danone Pty Ltd. The funder had no role in the study design, data collection, analysis, and interpretation of the study. There are no restrictions or delays on the timely publication of the results of the trial.

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Objectives and Study: An exploratory, multi-centre randomised, double-blind, placebo-controlled study was conducted in 290 healthy Thai infants aged 6-17 wks. The aim of the study was to evaluate the effects of two different doses of synbiotics on gut health in healthy infants.

Method: All infants eligible in formula fed groups started a 2-week run-in period with non-hydrolysed cow’s milk-based formula (control formula). Infants, who had successfully completed the run-in period, were randomised to receive either one of the two investigational formulas or the control formula for a double-blind period of 6 weeks. Investigational formulas were non-hydrolysed cow’s milk-based formula supplemented with 0.8g/100 ml scGOS/lcFOS with Bifidobacterium breve M-16V at a dose of either 1x 10⁴ cfu/ml (Syn4) or 1x10⁶ cfu/ml (Syn6). After the intervention period was completed, infants received control formula for a period of 2 weeks as the wash out period. Non-randomised exclusively breastfed infants were included as a reference group.

Results: Fecal pH was significantly lower and L-lactate concentrations were significantly higher in both Syn4 and Syn6 groups when compared to the control group after 6 weeks of intervention, similar to the level of reference group. Acetate was the main short chain fatty acid (SCFA) detected in all the intervention groups. After 6 weeks of intervention, fecal proportions of acetate were significantly increased and propionate and butyrate proportions were significantly decreased compared to the control in both the Syn4 and Syn6 groups. Stool frequency did not differ among the three intervention groups throughout the study. However, stool consistency was significantly softer in both the Syn4 and Syn6 groups during the intervention period when compared to the control group. No serious adverse events (SAEs) were recorded during the study. All formulae were well tolerated and all groups showed a comparable safety profile based on the number and severity of adverse events (AEs) and growth. The percentage of subjects experiencing any AEs was similar in both synbiotics groups and the control group.

Conclusion: With an infant-type bifidobacterial strain at a dose normally found in human milk, the synbiotic combination of B. breve M-16V and scGOS/lcFOS (9:1) created a gut environment similar to that of the reference group (healthy breastfed infants).

Disclosure of interest: This study was financially supported by Danone Nutricia Research. Shugui Wang, Rocio Martin and Jan Knol are the employees of Danone Nutricia Research.

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Longitudinal evolution of vitamins and carotenoids in human milk from mothers of term and preterm infants

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Background: Accurate quantification of preterm human milk (HM) vitamin composition is crucial for the formulation of adequate human milk fortifiers. Term HM vitamin contents are described but little is known on preterm breast milk vitamin and carotenoid composition.

Objectives and Study: To thoroughly quantify the longitudinal evolution of vitamins and carotenoids in preterm HM and to compare it to that of term HM.

Method: A prospective cohort, single-centre study (NCT #02052245) was conducted in the neonatal intensive care unit at the University Hospital in Lausanne. Twenty seven mothers of preterm infants (28-32 weeks gestational age) and thirty four mothers of term infants (> 37 weeks gestational age) participated to the study. Breast milk was collected every week on the first 8 weeks for all mothers and every second week for the preterm group during the following 8 weeks. Content of water soluble vitamins, fat soluble vitamins and carotenoids in HM samples was determined by applying 4 different methodologies covering the absolute quantification of vitamin A, B1, B2, B3, B6, B9, B12, and 5 main carotenoids β-carotene, β-cryptoxanthin, lutein, zeaxanthin and lycopene, either by microbiological based, liquid chromatography based or liquid chromatography-mass spectrometry based methodologies.

Results: Fat soluble vitamins, carotenoids and B12 concentrations decreased with lactation time but only significantly from week 1 to week 2 and/or week 3. Vitamin B2 concentration remained fairly stable along the studied lactation period. All other water soluble vitamin concentrations increased in the first weeks of lactation. Between-subject vitamin and carotenoid concentrations were very variable, but rarely significantly different in preterm and term HM. Levels of B2, B3 and B6 in this study were substantially different to those currently used as reference values.

Conclusion: This study provides up-to-date results on vitamin and carotenoid composition of preterm HM and suggests that the current reference values of vitamins B2, B3 and B6 may need revision.

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Objectives and Study: Nutrient fortification of donor human milk (e.g. more protein, energy, minerals) is currently recommended to feed very premature infants to support growth and neurodevelopment. Yet, there are concerns that challenging the immature gut with formula-based fortifiers may induce gut dysfunction and inflammation. Undigested protein and nutrients in the hindgut could potentially interact with microbes to negatively affect gut microbiota composition and gut health (e.g. more protein fermentation, diarrhea and necrotizing enterocolitis, NEC). Using preterm pigs as a model for preterm infants, we investigated if nutrient fortification of human donor milk, using different fortification products, affects the gut microbiota, diarrhea and NEC.

Method: Using preterm pigs fed human donor milk, three types of commercial products were tested: BC (intact bovine colostrum, Biofiber Damino), ENF (intact and partially hydrolyzed whey protein plus vegetable oils, Mead Johnson/Nutrilon) and NAN (extensively hydrolyzed protein and maltodextrin, Nestlé). In Exp 1, cesarean-delivered preterm pigs were fed unfortified milk or milk fortified with BC or ENF (+4.6 g protein/kg/d) from day 3-8. In Exp 2, preterm pigs were fed milk fortified with BC, ENF or NAN from day 1-5. Diarrhea and NEC lesions were recorded. Gastric, small intestinal, caecal and colonic contents were collected at the euthanasia, and the microbiota was sequenced using 16S rRNA gene sequencing. PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) was used to predict the metagenome of each sample based on 16S rRNA sequencing.

Results: In Exp 1, both groups of fortified pigs (BC, ENF) had lower Shannon diversity and higher bacterial load in gastric contents. In the caecum and colon, fortification affected the contents of microbial genes that are related to several metabolic pathways (aminoacyl-tRNA, penicillin/cephalosporin and lipopolysaccharide biosynthesis, nitrogen metabolism, bacterial toxin). There were no differences among groups in NEC but ENF fortification induced more severe diarrhea than BC and unfortified groups. In Exp 2, the NAN-fortified pigs had more diarrhea, higher NEC incidence, and lower Shannon diversity of microbiota in gut contents than BC-fortified pigs. Colonic microbial community of NAN pigs also differed from that in BC (more abundant Haemophilus and Lactobacillus). Staphylococcus was less abundant in ENF and NAN pigs relative to BC pigs in the gut.

Conclusion: Nutrient fortification of human donor milk may increase NEC sensitivity. This may be associated with altered microbial homeostasis and protein fermentation in both the stomach and the hindgut regions. Further research are required to characterize metabolites in the gut contents and identify the type of nutrient fortifier that best supports growth of preterm infants without inducing adverse effects on the gut microbiota and immature gut functions.
**Gut microbiota composition modulation by partly fermented infant formulae supplemented with prebiotics scGOS/lcFOS**

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**Objectives and Study:** Two recent randomized clinical trials have investigated the use of infant formula that combine a fermented formula (Lactofidus™) with the prebiotics scGOS/lcFOS (0.8 g/100 ml, 9:1) in several ratios of fermented formula on base powder (i.e. 15/85, 30/70, and 50/50). These studies confirmed the safe use of such partly fermented formulae (trials registered under Netherlands Trial registry NTR2521 & NTR3455). The objective of the combined analysis was to investigate the effect of the three partly fermented (Experimental) formulae in the infant gut microbiota composition compared to the control products from both trials, i.e. a formula with prebiotics, a formula with only ferment addition, and a formula without either prebiotics or ferment, as well as to a breast-fed reference group. In each of these seven study arms stool samples were selected from those collected on the day of randomization or the day thereafter (0–4 weeks of age) and at the end of intervention (17 weeks of age).

**Method:** For 30 subjects with a complete sample set per study arm targeted physiological parameters (such as fecal pH, levels of short chain fatty acids, and levels of sIgA) were determined and untargeted 16S rRNA gene amplicon sequencing was performed.

**Results:** At the end of the interventions the infants consuming one of the Experimental products showed, in contrast to the infants consuming control products without prebiotics, the saccharolytic fermentation profile observed in feces of breast-fed infants and in the infants consuming the formula containing prebiotics, such as a lower pH, higher levels of acetic acid, higher levels of sIgA. No dose response of the ferment addition was observed.

In both trials, microbiota community profiling by 16S rRNA gene amplicon sequencing showed separately that the Experimental products did not change the entire microbiota community structure. However, several bacterial groups did consistently change when comparing an Experimental with a Control arm. Most of these changes were in line with the results of the physiological parameters. Of particular interest were three genera (*Blautia*, an uncultured taxon within the Clostridiales order, and an uncultured taxon within the Erysipelotrichales order) that were found in both trials to be specifically reduced in all Experimental arms as well as in the breast-fed reference arm. These genera were not reduced in the gut microbiota of infants consuming any of the control formulae.

**Conclusion:** The observed relative decrease of a *Blautia* sp. and two uncultured taxa (Clostridiales and Erysipelotrichales relatives) in infants consuming one of the Experimental formulae (i.e. partly fermented infant formula and prebiotics scGOS/lcFOS), that was consistent over two independent trials, is more similar to levels observed in breast-fed infants. These microbial taxa did not change when consuming only the prebiotics or only the fermented formula. Further research is needed to establish the biological relevance of these findings, but given the specific acetogenic pathways known for cultured members of the *Blautia* genus, the overall microbiota metabolism in the gut is expected to be impacted and resulting in a more balanced fermentation profile.

**Disclosure of interest:** ST, GR and JK are employees of Danone Nutricia Early Life Nutrition, which funded the studies.

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Human milk oligosaccharides modify immune responses in vitro

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Objectives and Study: Human milk oligosaccharides (HMOs) comprise a group of structurally complex, unconjugated glycans highly abundant in human breastmilk. HMOs are not digested in the gastrointestinal tract and reach the colon intact or are absorbed in small quantities and reach the systemic circulation and are excreted in urine. HMOs can bind to cell surface receptors and modulate neonatal immunity by altering host epithelial and immune cell responses in the infant gut, or act as soluble decoy receptors to block the attachment of various microbial pathogens to cell surface receptors. In this study, we investigated which HMOs bind to cell surface receptors and estimated the amount of HMOs that reach the circulation in order to develop in vitro tools to study potential HMO signaling in the immune system.

Methods: A glycan array with 60 synthesized oligosaccharides was screened with recombinant human proteins that are described in literature to recognize carbohydrate moieties (Galectin 3 and 9, Siglec 9 and DC-SIGN). After verifying binding of HMOs to these receptors we used galactooligosaccharides (GOS) and 2'-fucosyllactose (2'-FL) to check whether these glycans compete for binding to other HMOs. Next, we used porcine enteroids grown in transwell permeable supports to estimate the amount of HMOs that can cross the intestinal epithelium and reach the circulation, using 2'-FL and lactose as representative glycans. We subsequently used corresponding amounts of HMOs isolated from pooled human milk samples to stimulate Peripheral Blood Mononuclear Cells (PBMCs) and measure immune responses by means of PCR and ELISA for certain markers.

Results: By using HMO arrays we found that various HMOs can bind immune cell receptors with different affinities. Especially in the case of galectins, 2'-FL or GOS do not seem to compete for receptor binding to the glycan array, making it unlikely that these oligosaccharides exert a function through binding to galectins.

Porcine enteroids, isolated and differentiated from slaughterhouse material were seeded on transwell supports. 2'-FL or lactose were added on the apical compartment and after 24h concentrations of glycans were measured in the basolateral compartment. Approximately 1% of 2'-FL and lactose was detected in the basolateral compartment. This, along with existing literature that reports the detection of HMOs in urine of breast fed infants, suggests that HMOs may be absorbed from the intestine albeit in variable amounts.

PBMCs isolated from three donors were then incubated with HMOs isolated from pooled human milk samples at concentrations determined in the previous experiment. HMOs were able to downregulate production of TNFa, CCL2 (MCP-1), IL1a and IL1Ra as measured by PCR and ELISA.

Conclusion: HMOs can cross the epithelial barrier in the intestine and reach the systemic circulation. Although the percentage of absorption is relatively small, the amount of HMOs that reaches the circulation is sufficient to exert anti-inflammatory effects on immune cells isolated from human blood by binding to immune receptors. These results correspond with data from published clinical trials, making PBMCs a relevant in vitro system to study the effects of HMOs on the immune system.
The biological function of milk-derived miRNAs

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Objectives and Study: Milk is the main source of nutrition for newborn and infants. Breastfeeding is known to be one of the most valuable contributors to infant health. Breastfeeding is associated with reduced risk of infection, immune mediated disorders, obesity and even cancer. Beneficial effects of human breast milk on health may be partly associated to its microRNAs (miRNAs) composition. Milk contains a variety of miRNAs that can be transferred to the infant. We have identified that the highly expressed miRNA in milk are known as beneficial miRNA related to immune system development and disease prevention such as mir148a-3p, mir146 and 99a.

Method: Milk derived-miRNAs were isolated from the skim and fat layer of milk. Normal and tumor cells were incubated with exosomes and fat globules derived from milk. The entrance of milk derived RNA was show by RNA staining and immunofluorescence detection. The miRNA expression in these cells was analyzed by quantitive real time PCR (qRT-PCR). Expression of target genes of milk miRNA was analyzed by qRT-PCR. Proliferation, differentiation and protein expression were analyzed in cells incubated with milk miRNAs.

Results: We demonstrate that human milk miRNA in exosomes and in the fat layer are taken up by intestinal epithelial cells (CRL1831 and CRL841) and tumor colonic cells (Lim 1215 and LS123). We showed that following incubation of milk-derived miRNAs with normal and tumor colonic cells the expression of miRNAs in the cells was modify. For example miRNA-148a, and mir-320 were upregulated. The expression of bcl-X, DNA methyltransferase1 and 3, target genes of miRNA-148a were down regulated in cells with up-regulation of miR-148a after incubation with milk-derived miRNA. Moreover, milk-derived miRNAs changed the expression of proteins such as collagen and activate the MAPK pathway. We also demonstrated that milk derived miRNAs increased normal colonic cell proliferation approximately by two fold at 72 hours and by 3 folds at 92 hours. In contrast, milk derived miRNAs into exosomes have not effect on proliferation of tumor cells.

Conclusion: Our results reinforce previous findings on the importance of miRNA in breast milk. Furthermore, this study provides a biologic mechanism for the beneficial effect of milk-derived miRNAs. Our results can give the experimental basis in attempt to add beneficial miRNA from milk to infant formula.

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NUTRITION - Basic science

N-P-002

Pancreatic enzyme maturation is delayed and not affected by the first enteral nutrition in preterm pigs

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Objectives and Study: Preterm infants have an immature digestive system, predisposing them to short- and long-term complications, including intolerance to enteral feeding. Thus, optimal feeding strategies are required to prevent life-threatening conditions like severe diarrhoea and necrotising enterocolitis (NEC). Pancreatic enzymes are important for digestion but little is known about the postnatal development of the exocrine pancreas. Using preterm pigs as models for preterm infants, we hypothesized that: 1) postnatal development of the exocrine pancreas is delayed after preterm birth, and 2) minimal enteral nutrition during the first days of life provides better stimulation of the exocrine pancreas function relative to total parenteral nutrition.

Method: Pigs were delivered by caesarean section preterm (90% gestation) or at full term, and were nurtured during the first 5 days with total parenteral nutrition (TPN) or with parenteral nutrition plus minimal enteral nutrition (MEN) with bovine colostrum. From day 6, all pigs were fed full enteral nutrition with bovine milk until postnatal day 26. Pancreatic samples were collected on days 1, 5 or 26 from both preterm and term pigs (n=116). Trypsin and amylase activities were analysed in tissue homogenates. Protein content was measured and used to calculate the relative amount of the enzymes. Data were analyzed for the same gestational age between treatments (e.g. MEN vs TPN, Tukey's post-hoc test, P<0.05 indicated with different letters) and within treatments between different gestational ages (e.g. Preterm vs Term, Sidak's post-hoc test, P<0.05 indicated with *) (see Figure).

Results: Pancreatic trypsin and amylase concentrations increased with age in preterm piglets, especially by 26 days (P<0.05), with no differences between the diet regimens (TPN vs MEN) (see Figure). Term piglets showed higher relative trypsin activity levels at birth and these were maintained with advancing age, but 5 d old TPN-fed term pigs had higher levels compared with MEN (P<0.05). Amylase activity was low at birth in term piglets and increased with age (P<0.05). At 5 days, term TPN-fed piglets failed to increase their amylase activity relative to birth. Pancreatic trypsin was lower in preterm than in term piglets at 5 days after birth (P<0.05) but amylase was higher in preterm than in term piglets at day 26 (P<0.05).

Conclusion: Pancreatic trypsin and amylase relative activities increased with age in preterm piglets and by day 26 the enzyme levels converged to those in term piglets. TPN or MEN nutrition for the first 5 days only had effects on enzyme levels in term piglets, indicating that the effects of the first diet depends on gestational age at birth. Increased trypsin activity in term, 5 d-old TPN-fed piglets may be explained by lack of enteral stimuli to stimulate pancreatic secretion. Conversely, amylase activity level was very low at birth and increased with age. Lower amylase activity in term, 5 d-old TPN-fed piglets may be explained by lack of enteral stimuli to increase enzyme production. We conclude that pancreatic trypsin and amylase activities depend on both gestational age at birth and postnatal age and have different sensitivities to the first feeding.
Pancreatic trypsin and amylase enzyme levels in preterm and term pigs fed with TPN or MEN

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Objective and Study: Preterm birth interrupts the intrauterine maturation of organs and may impair the normal brain development in the postnatal period. The brain develops rapidly in the perinatal period and may or may not be highly susceptible to environmental changes such as birth, feeding and microbial colonization. Prematurity in pigs is associated with neurodevelopmental deficits, but it is unclear how these deficits may be determined by postnatal age (PNA), postconceptional age (PCA) and environmental factors. Using preterm pigs as a model for preterm infants, we hypothesized that preterm birth impairs structural and functional brain development after birth, although mainly influenced by PCA.

Method: Pigs were derived by cesarean section at 90% gestation (PRETERM, n=43) or full term (TERM, n=41) and randomized to groups euthanized either at birth (d1) or after 11d (n=17-24 per group) (Fig. 1A). Clinical, para-clinical and brain outcomes were measured at d1 and d11. Functional brain outcomes included basic motor skills (first eyelid opening, first stand and first walk), independent drinking, balance and walking coordination (gait analysis). Structural brain outcomes included wet weight of the brain and selected brain regions, permeability of the blood-brain barrier and biochemistry of blood and cerebrospinal fluid (CSF).
**Results:** Term pigs showed higher weight gain than preterm pigs, despite identical nutrient intakes (+30%, p< 0.05). Comparison of preterm and term pigs at the same PCA showed no difference in absolute or relative weights of the entire brain (Fig. 1B) and brain regions between d11 preterm and d1 term pigs. Only striatum weight was higher in d11 preterm versus d1 term pigs (p< 0.05). The brain hydration level was higher in preterm versus term pigs at both ages (p< 0.05). At PNA d11, weights of the entire brain and cerebrum, cerebellum and brain stem were higher in term pigs relative to preterm pigs. For hippocampus, preterm pigs had lower weights than term pigs at d1 but not at d11 (p< 0.05), indicating a postnatal catch-up growth of the preterm hippocampus. Lactate concentration in plasma and CSF of preterm pigs mimicked that in term pigs, whereas glucose levels were lower at both ages. The blood-brain barrier permeability (measured by raffinose levels in CSF after an i.v. bolus) was highest in preterm pigs (p< 0.01). Finally, preterm pigs showed a delay in time to learn to drink and required longer time for first eyelid opening, first stand and first walk. In the gait analysis, term pigs had longer normalized stride and step length, while preterm pigs had higher normalized maximum stride height.

**Conclusion:** The lack of difference in brain weights between d11 preterm and d1 term pigs indicates that PCA, rather than environmental factors and PNA, is the main determinant of brain growth. The functional tests confirmed that preterm pigs showed impaired motor coordination, indicating reduced neuro-motoric maturation. Despite the delays in brain development in preterm pigs, postnatal maturation occurred rapidly with PNA, with some parameters reaching that of term newborns at the corresponding PNA (d11). The developing brain of both preterm and term newborns may be relatively resilient to environmental stimuli such as birth, nutrition and microbial colonization.
Specific bacteria and yeast transferred from mother to the infant gut through lactation

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Objectives and Study: Maternal microbiota is being recognized as one of the essential factors determining maternal-child health outcomes, which would also be affected by perinatal factors. At birth maternal microbes contact with the infant through delivery canal and then, this inoculum is supported by breastfeeding. Moreover other genetics, environmental factors and diet may also influence the microbiota development. The aim of this work is to isolate and identify specific bacteria and yeast shared between breast milk and infant fecal samples in order to demonstrate the specific transfers between each mother-infant pair.

Methods: Mother-infant samples (maternal and infant feces, breast milk) were collected at 2 months after delivery. Data related to mode of delivery, and anthropometric records. Microbiota composition and activity assessment by conventional bacterial culture, 16S rRNA gene sequencing, quantitative PCR, and denaturing gradient gel electrophoresis (DGGE)

Results: Shared features between the microbiota detected in maternal-infant pair and breast milk were found suggesting a specific microbial transfer during lactation. Specific strains belonging to \textit{Bacteroides}, \textit{Bifidobacterium}, \textit{Staphylococcus} and \textit{Enterococcus} genus were isolated from maternal-infant gut and specific strains of \textit{Staphylococcus}, \textit{Lactobacillus}, \textit{Enterobacter} and \textit{Acinetobacter} from paired breast milk at 2 months of age. \textit{Rhodotorula} and \textit{Candida} were the most isolated yeast from milk and maternal-infant gut. DGGE profiles showed higher diversity in maternal gut compared to infant gut and breast milk. \textit{Bacteroides} and \textit{Bifidobacterium} strains were shared between maternal and infant gut identified by DGGE

Conclusion: Specific breast milk bacteria and yeast would play a key role on the infant microbiota development.

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Cytokine characterization and growth factors in maternal milk depending on delivery mode

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Objectives and Study: Breast milk (BM) is considered as the reference for infant’s nutrition. The complex composition of BM may exert specific effects on their immunological competence, particularly during the first months of lactation when breast milk is the sole source of food. The role of several bioactive components of BM such as cytokines, and growth factors is poorly known, but they might be implicated in the immune response development. The aim of our study was to study the impact of mode of delivery in the cytokines, and growth factors profiles in BM samples.

Methods: A longitudinal prospective study of characterization of cytokines and neurotrophic growth factors was conducted in BM samples (colostrum and mature milk) from 40 healthy mothers. Cytokines were analyzed by Protein array (Ray Bio® Human Cytokine Array G6. Ray Biotech, Inc) consisting of 60 different antibodies directed against them.

Results: Vaginal and non elective C-section showed the higher expression of cytokines (Interferon gamma (IFNγ), IL (Interleukine) IL-1-alfa, IL-1 beta, IL-4, IL-5, IL-6, IL-7, and TNF-alfa), and growth factors (Brain-derived neurotrophic factor (BDNF), Ciliary neurotrophic factor (CNTF), Glial cell line-derived neurotrophic factor (GDNF) and Neurotrofina 3 (NT-3)) profiles compared to those observed in elective C-section.

Conclusion: Our study is the first to provide the influence of mode of delivery on cytokine, chemokine, and growth factors in human milk that may have potential implications for neonatal health programing.

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**NUTRITION - Basic science**

N-P-006

**Effects of fatty acids on intestinal barrier function by modulating endoplasmic reticulum stress (ERS) - induced autophagy**

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**Objectives and Study:** The fatty acid pattern is considered to have effects on intestinal epithelial barrier function (IEF). The aim of this study is to explore whether endoplasmic reticulum stress (ERS)-induced autophagy is involved in the mechanism.

**Method:** Caco-2 cell monolayers were established and were divided into six groups, as follows: Con (control), TM (tunicamycin), P (100 µM palmitic acid), PO (40 µM palmitic acid+60µM oleic acid), POL (40 µM palmitic acid+40 µM oleic acid+20µM linoleic acid) and POA (40 µM palmitic acid+40 µM oleic acid+20µM linolenic acid). The barrier function of Caco-2 monolayers was evaluated by measuring transepithelial electrical resistance (TER) and FITC-Dextran 40,000 Da transmembrane flux at 24 hours after various treatment. Besides, autolysosomes were observed by fluorescence microscope. Protein and mRNA levels of sXBP1, BIP, UCP2, PERK, LC3A/B, Beclin1 and P62 were quantified by western blot and quantitative polymerase chain reaction (qPCR), respectively.

**Results:** P and PO induce IEF impairment as measured by a significant decrease in TER (369.7±8.7 and 654.0±8.2 vs 809.7±13.2 Ω·cm², P< 0.05) and a significant increase in dextran permeability (11609.7±122.9 and 5617.0±197.9 vs 4049.2±177.6 ng/ml, P< 0.001), compared to Con. POL and POA alleviate IEF impairment significantly by improving the decrease in TER and increase in dextran permeability. The accumulation of autophagosomes was detected in POL and POA by fluorescence microscope. Protein and mRNA levels of sXBP1, BIP, UCP2, PERK, LC3A/B, Beclin1 and P62 were quantified by western blot and quantitative polymerase chain reaction (qPCR), respectively.

**Conclusion:** The results suggested that partial replacement with polyunsaturated fatty acids (PUFA) ameliorated palmitic acid-induced IEF impairment via ERS-induced autophagy.
[Fig. Partial replacement with PUFA ameliorated palmitic acid-induced IEF impairment.]
In vitro consumption and utilization of different Microbiota Accessible Carbohydrates (MACs) by key microbial components of the infant microbiome

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Objectives and Study: Several essential groups of commensals found in the infant gut such as Bacteroides and Akkermansia, have been described as effective utilizers of Human Milk Oligosaccharides (HMOs) which are a class of Microbiota Accessible Carbohydrates (MACs). Particularly, members of the genus Bacteroides constitute a key genus in the gut microbiota, and studies have confirmed that Bacteroides may also dominate the intestinal microbiota of vaginally born infants. Bacteroides are known for their ability to utilize a wide variety of polysaccharides from the intestinal environment, such as xylan and starch as well as host-derived glycans, especially those associated with intestinal mucus. This extraordinary saccharolytic ability is attributable to specialized genes encoded by the polysaccharide utilization loci (PULs) within the Bacteroides genomes. The aim of this study was to monitor the consumption of a variety of purified MACs by Bacteroides thetaiotaomicron (Bt) and Akkermansia muciniphila (Am). As a comparison we also monitored the rate of consumption of simple glucose.

Methods: B. thetaiotaomicron ATCC 29148 and A. muciniphila ATCC BAA835 were cultivated in Minimal Medium containing the different carbon sources at a final concentration of 1.5% for MACs or 0.5% for glucose. Cultures were performed in 96-well plates, in triplicate, under anaerobic conditions. The bacterial growth were determined by measuring the optical densities (OD) at 600nm at the start, after 24h, 48h and 72h of growth.

Results: We found that depending on the purification and preparation of MACs mixtures we are able to obtain a good growth of Bt, similar to what was observed in the presence of glucose. However, the maximum OD reached with a delay of 24 hours compared to glucose. Interestingly some other MACs mixtures seems to selectively stimulate specifically the growth of Ak. This open very important perspectives for the personalized modulation of infant microbiota.

Conclusions: This study shows that MACs might have a similar function to HMO by stimulating infant microbiota in vitro. In addition, the data presented here suggest the possibility to precisely modulate the infant microbiota by changing the MACs composition and pave the way of important innovative prebiotic treatment.

Disclosure of interest: Kunz, Adesokan, and Steenhout are affiliated with Gnubiotics Sciences
Leptin detection in human milk and formulas using nanoflow liquid chromatography (nLC) and high-resolution mass spectrometry (HRMS)

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Objective and Study: Breast milk contains bioactive components, which play an important biological role for the newborn. Leptin, insulin and adiponectin are some of the hormones that have a role in energy balance regulation, food intake, and child body composition.

Leptin is an anorexigenic hormone that acts on neuronal cells of the hypothalamus and it is produced by adipocytes, human placenta and mammary glands.

Leptin has been detected in breast milk (BM), using different techniques such as Elisa or radioimmunoassay (RIA), but its presence in formula milk (FM) is still controversial.

In order to investigate the presence of leptin in breastmilk and formulas, we aimed to develop a selective nanoflow liquid chromatography (nLC) and high-resolution mass spectrometry (HRMS) method to evaluate leptin content in different milk matrices.

Methods: Breast milk (1-5 mL) was collected according to the availability of each mother in the first 20-30 days postpartum. The human milk was prepared and purified following a immunoaffinity protocol in order to detect leptin as intact protein (in concentrations < 0.1 fM), which was extensively characterized by high resolution mass spectrometry in order to evaluate interferences. Full mass spectrometry (MS and CID/ETD MS/MS) of multicharged positive ions of standard proteins were acquired. A top-down approach was used with the aim of reduce to a minimum sample manipulation. Accuracy, precision, LLOQ and linearity were then assessed. Then, the sample eluted from immunoaffinity columns was digested with trypsin in order to detect marker peptides and characterized by high resolution mass spectrometry.

Results: Intact leptin was not identified neither in breast milk nor in infant formulas. After digestion of purified samples leptin was quantified in samples (besides identification of interfering unknown proteins: lactoferrin and β-lactoglobulin). In two different commercial infant formulas leptin resulted < LLOQ (1 µg/L). Regarding human breast milk samples, leptin concentration was quantified, obtaining values of 6-7 µg/L.

Figure reports extracted chromatograms of Leptin (m/z 708 and 764 ions) in breast milk versus two different infant formula samples.
Conclusion: Our study, the first of this kind, seem to confirm that leptin is present in breast milk but not in formulas. The developed method displays a better sensitivity compared to literature and can be used for milk and plasma leptin dosage. Data acquisition of new samples for statistical purposes is being implemented.
Sequence based high-resolution profiling of Bacteroides species and strains in the microbiome of caesarean section and vaginally delivered infants

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Objectives and Study: Proper establishment of infant gut microbiome plays an essential role in the foundations of human health. Mode of delivery (vaginal birth vs. c-section), as well as mode of feeding (breastfeeding vs. formula) have been shown to greatly influence the presence and abundance of different taxa in the infant gut. Previous studies showed that bacteria from the Bacteroides genus (Bact) are among the first to populate the infant gut. Aim of this study was to analyze at high resolution (species and strain level) presence and abundance of Bacteroides genus members in the infant gut microbiome, and examine the correlations with the mode of delivery as well as feeding methods.

Methods: Using novel, high resolution quantitative sequencing method, we analyzed the presence and abundance of 14 specific Bact species, in the feces of infants born vaginally (n=26) vs. c-section (n=30), at 1, 3, 7, and 12 months of age. Further, the same method was used to detect and analyzed 4 specific Bact strains. For bioinformatics analysis, blast was used as the alignment tool, comparing each of the query datasets to each of the sample libraries, and setting parameters for optimal, tight alignments favoring identity matching versus homology matching.

Results: Out of 14 targeted Bacteroides species, 3 were detected at Month 1 (B. vulgatus, B. fragilis, and B. dorei), 10 at month 3 (B. xylanisolvens, B. vulgatus, B. uniformis, B. thetaotaomicron, B. stercoris, B. ovatus, B. intestinalis, B. fragilis, B. dorei, and B. caccae) and 7 at month 7 (B. xylanisolvens, B. vulgatus, B. uniformis, B. thetaotaomicron, B. stercoris, B. ovatus, B. fragilis) and 10 at Month 12 (B. xylanisolvens, B. vulgatus, B. uniformis, B. thetaotaomicron, B. stercoris, B. ovatus, B. intestinalis, B. fragilis, B. dorei, and B. caccae). Among all samples, B. vulgatus and B. fragilis were the most prevalent species. In accordance with previously published data, we show that c-section delivery and exclusive breast-feeding are associated with relatively low abundance of Bacteroides in the infant stool: Bact species were detected in 73% vaginal and 16% c-section samples; and within the vaginal cohort, there were more Bact present in formula-fed infants, then in breastfed infants (only 1 breastfed sample contained Bact species, while 18 formula-fed samples contained various Bacteroides species). Additionally, we were able to identify 4 specific bacteroides strains: B. fragilis YCH46, B. fragilis S14, B. distasonis ACCT 8503, and B. vulgatus ATCC 8482. B. vulgatus ATCC 8482 was the most prevalent one.

Conclusions: This study represents the first species and strain level analysis of Bacteroides in infant microbiome. Considering that the absence of Bacteroides species is associated with gastrointestinal symptoms in infants, and that potentiating the growth of these bacteria may be of clinical importance, being able to monitor dynamics of individual Bact species and strains within the microbiome would be of great importance. Human milk oligosaccharides (HMOs) from mother's milk are are known to be consumed by Bacteroides. Supplementation of formula with specific HMOs may potentiate the growth of Bacteroides. Given that ATCC 8482 strain was shown to be one of the high HMO consumers, it could be used as a marker of HMO consumption.

Disclosure of Interest: Adesokan A. and Kunz JP are affiliated with Gnubiotics Sciences

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Strain level analysis of bifidobacteria in the microbiome of early intervention formula-fed infants in the first year of life

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Objectives and Study: Gut-residing bacteria from the Bifidobacterium genus play an important role in infant metabolism and health. It is known that human milk oligosaccharides (HMOs), from breast milk, are essential for the growth of specific microbiome taxa, including Bifidobacterium members. Although many studies have explored the presence and abundance of Bifidobacterium members in infant gut, there is no data on specific Bifidobacterium strains and their possible differential role in infant gut. In the present study, we analyzed strain level of Bifidobacterium genus in the infant gut, and how specific strains are related to the mode of feeding.

Methods: Using novel, high resolution quantitative sequencing method, we analyzed the presence and abundance of specific Bifidobacterium strains, in the feces of infants that were either breastfed (BF n=18), fed with formula (F n=20) or with bifido-supplemented formula (F+ n=20), at 1, 3, 7, and 12 months of age. Bioinformatics analysis was done using a curated database and the BESTFIT algorithm, which utilizes BLAST and a tiered approach combining percent identity and alignment overlap cutoffs.

Results: With our sequencing method we were able to detect 55 Bifidobacterium strains across all samples. Among the three cohorts, F+ group had the highest and BF group the lowest diversity and abundance of bifidobacteria strains. 14 of the detected strains, with prominent abundance, belonged to the B. longum species. The most highly expressed among B. longum were: NCC2705, KACC-91563, GT15, DJO10A, BG7, and 105-A. Additionally, there were 11 highly abundant strains which belonged to the B. breve species. Most prominent ones were: S27, LMC520, and BR3. B. Breve BR3 strain was added as supplement in the F+ formula, thus the high abundance in the F+ cohort was expected.

Conclusion: This study represents the first strain level analysis of bifidobacteria in infant microbiome. It shows that our methodology permits for deeper look at specific bifidobacteria strains in the human gut. Given the importance of these bacteria in human health, and their direct link with the HMOs, this could serve as an important tool for dissecting the dynamics of bifidobacteria in relation to infant nutrition and metabolism.

Disclosure of interest: Adesokan A. and Kunz JP are affiliated with Gnubiotics Sciences

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**NUTRITION - Basic science**

N-P-011

Lactoferrin and butyrate exert beneficial effects on human primary adipocyte function in vitro

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**Objectives and Study:** With the worldwide obesity epidemic progressing and high prevalence of comorbidities, there is a strong need for nutritional strategies early in life to reduce the risk of becoming overweight. Adipocyte function plays a crucial role in lipid metabolism and fat storage and therefore might be a promising target for nutritional interventions. Previous studies in rodent models have suggested anti-adipogenic activity of lactoferrin, a key bioactive compound in milk, and butyrate, a bacterial colonic fermentation product. Since evidence from human adipocytes is limited, we aimed to study the effect of lactoferrin and butyrate on human primary adipocyte function in vitro.

**Methods:** Human primary subcutaneous adipocytes were used for all assays. Bovine lactoferrin (Lf) and sodium butyrate (SB) were tested in triplicate in three different concentrations (300 nM, 5 µM and 10 µM for Lf, and 0.5, 1 and 3 mM for SB). To assess lipolysis, differentiated adipocytes were exposed to Lf and SB for 3 hours, after which glycerol concentrations were determined in the media. Adipogenesis was studied by exposing adipocytes to Lf and SB during differentiation and maintenance over 12 days, followed by measuring triglycerides in lysed cells and assessing FAB4, PPARγ and C/EBPa gene expression. Radio-labeled glucose uptake was determined in lysed cells after 2 hour incubation of differentiated adipocytes with Lf and SB and 2-deoxyglucose/3H-2-deoxyglucose. UCP-1 gene expression in mature adipocytes was measured by qRT-PCR after Lf and SB stimulation for two weeks. Statistical significance was evaluated using a t-test (p< 0.05).

**Results:** Lf dose-dependently increased lipolytic activity in human primary adipocytes in all three concentrations tested. Exposure to both Lf and SB strongly inhibited lipid accumulation and down-regulated the expression of genes involved in adipocyte maturation and lipid storage. Furthermore, exposure of adipocytes to Lf, but to a lesser extent SB, also stimulated glucose uptake and resulted in slightly increased UCP-1 gene expression, a brown fat phenotype marker.

**Conclusion:** Lf and SB both consistently and significantly modulated human primary adipocyte function in vitro. The observed effects on biological processes in adipocytes such as lipolysis, adipogenesis, glucose uptake and browning, may contribute to elevated metabolic activity and decreased adipogenic potential in vivo. These properties are of particular interest in view of reducing the risk of lipid accumulation and developing obesity.

This study was financially supported by Mead Johnson Nutrition.

**Disclosure of interest:** G. Gross and E.A.F. van Tol are employees of Mead Johnson Nutrition. M.J. Van Kanegan and J. Nicoll are employees of Zen-Bio, Inc.

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Preparation of low-glycemic Indian Vetch-Wheat composite flour and evaluation of post-prandial glycemic response

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Introduction: Bread (Chapatti), a staple food in Pakistan is consumed as a source of energy and nutrients in the diet of common man. Legumes are known to be effective in glycemic control because of their slow releasing carbohydrate mechanism and high fiber content. Therefore, increased use of legumes as replacement of rapidly digested carbohydrate in daily intake is expected to improve glycemic control and incidence of diabetes in vulnerable individuals. We aimed to test our hypothesis by preparing a composite flour with different percentages of wheat and indian vetch.

Methods: The present study was conducted in two phases. During first phase composite flours were prepared and their chemical, functional and rheological properties were analyzed. In second phase, chapattis were prepared from composite flour blends and the effect of these chapattis on post-prandial glycemic response in healthy subjects was evaluated. The study was conducted at Department of Food Science & Human Nutrition and Rahmat Flour Mills Lahore.

Results: The results from first phase showed that Indian Vetch could safely be used to supplement chapattis after detoxification. It could be added up to the level of 20% in chapattis without causing any deleterious effect on its sensory and nutritional characteristics. Results from second phase showed significant differences in glycaemic response after consuming Chapattis from 100% wheat flour vs Chapattis from 20% mixture of Indian Vetch composite flour. (See table 1) The analysis of variance pertaining to the glycemic index of different types of Chapattis indicated that the glycemic index of chapattis was significantly different with each other. The highest score for G.I is for Normal chapatti (65.13±6.53) and the lowest for 20% composite flour chapatti (55.10±4.38).

Conclusion: Composite flours containing wheat and legumes blend can offer potential benefits. On one hand legumes can be source of protein and on other hand they can contribute in lowering the glycemic index of commonly consumed foods for example chapatti. Further studies are needed to see the long-term effects in healthy and diabetic patients.

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Time Interval (minutes)</th>
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<td>0</td>
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<tr>
<td>T0</td>
<td>4.77±0.08</td>
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<tr>
<td>T20</td>
<td>5.08±0.07</td>
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[: Blood glucose concentration (mmol/L) after consu]
Objective and Study: Atherosclerosis and cardiovascular diseases are one of the top-leading health problems worldwide. There is a compelling evidence that atherogenesis begins in childhood. Early identification of children at risk of atherosclerosis may allow primary preventive interventions. Molecular markers of endothelial dysfunction including soluble cell adhesion molecules: sE-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are considered as an early marker of atherosclerosis. The aim of the study was to determine the level of soluble adhesion molecules in the two groups of children: aged 18-30 months and 5-6 years old.

Method: The research was performed in two stages. Initially we recruited 50 children into our study. In the first stage volunteered 41 children (22 males and 19 females) aged from 18 to 30 months from the initial group. The follow-up assessment was performed in 47 children (26 males and 21 females) aged from 5 to 6 years old from the initial study group. Medical history of breast-feeding after delivery, lipid disorders and atherosclerosis risk factors in the family was collected. All children underwent anthropometric measures and blood sampling. The concentrations of (sICAM-1), (sVCAM-1) and sE-selectin were determined by ELISA method, with the application of kits human sICAM-1 BMS201, human sVCAM-1 BMS232, human sE-selectin BMS205. The study was approved by the local bioethical committee.

Results: Serum concentration of sVCAM-1 was significantly higher in children aged 18-30 months (1702.67±671.24ng/ml) than in children aged 5-6 years old (1516.07±791.87ng/ml) (p<0.01). Serum concentration of sICAM-1 was significantly lower in children aged 18-30 months (371.06±85.16ng/ml) than in children aged 5-6 years old (404.09±75.44ng/ml) (p<0.05). Serum E-selectin was significantly increased in 18-30 months old children (77.58±38.34ng/ml) compared to 5-6 years old children (47.44±35.57ng/ml) (p<0.0001). There were no significant differences in the analyzed parameters with the reference to patient's gender, duration of breast-feeding, anthropometric measures and family history for atherosclerosis.

Conclusion: Our result suggest that soluble cell adhesion molecules may predict early atherosclerosis in children. Further studies are needed to firmly establish the role of soluble adhesion molecules in the atherogenesis.
Objectives and Study: DNA-sequencing-based analyses of the gut microbiome are becoming increasingly important both for scientific studies as well as medical diagnostics. The development and stabilization of the infant gut microbiome is the major field for this method within paediatrics, but the method is the same for any type of human stool sample. A standard for scientific studies is deep-freezing of stool samples, which requires keeping samples frozen until processing and is more elaborate with regard to taking samples by patients at home. Therefore, direct shipping of samples to diagnostics laboratories by mail at room temperature is often applied. However, the outside temperature and time in the mail make this method inappropriate for scientific studies. ‘Freezing’ the microbial composition by inactivating the microorganisms and stabilization of DNA is a possibility to make shipping easier and keep results accurate. Commercial kits for DNA protection in stool samples are available from different providers and were compared in this study. DNA extraction from stool samples is the next step in the processing pipeline. In this study we also compared different stool DNA extraction kits.

Methods: Stool samples for the comparative stabilization and protection study were provided by the same adult donor; samples for all kits as well as controls were taken from the same faeces. For probing different stool extraction kits, a microbial community standard was used as starting material for subsequent DNA extractions. After DNA extraction a PCR amplification of the V3-V4 of the 16S rDNA was carried out and the resulting pool of fragments was subjected to Next Gen Sequencing. The obtained sequences were mapped against a reference database and from counting the hits for each entry the relative abundance within a sample was calculated.

Results: We compared the data obtained with stool sampling and DNA stabilization kits from two suppliers with those obtained for control samples of the same faeces that were immediately deep-frozen or shipped at room temperature. Our results indicate that especially Ruminococcaceae are selectively favored when DNA protection solution is used for sample storage and shipping. Bacteroidaceae and Lachnospiraceae showed the highest relative abundance in samples that were shipped untreated at room temperature or were deep-frozen, respectively. In contrast to untreated fresh and frozen samples, the samples that were subjected to DNA protection displayed a much greater variance between A and B samples. Performing DNA extraction from a microbial community standard showed that no DNA extraction kit gave the ultimate results. Both tested kits showed a bias. However, the results obtained with one kit were closer to the expected values.

Conclusion: Since preservation of stool samples by using microbial inactivation and DNA protection solutions alters the results of microbial composition analyses compared to both fresh and deep-frozen samples and since consistency between samples is not guaranteed, this technique cannot be applied for quantitative scientific studies. Both tested DNA extraction kits were somewhat biased. The data suggest one kit for subsequent preparations. More importantly, the data show that it is essential to stay with one kit and one pipeline throughout a study.

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Impact of structure of ruminant casein curd on digestive behaviour under infant gastric conditions

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Objectives and Study: Whey-based formulas are generally recommended for infants over casein based formula in part because they promote digestion and faster gastric emptying. This is based on the acid induced precipitation of casein within the stomach, which is assumed to slow digestion and gastric emptying. The curd structure of cow milk and goat milk produced by rennet are very different (Storry et al, 1983 J Dairy Res 50, 215). We hypothesise the casein in formula made from goat milk will behave very differently under gastric digestion conditions of infants than casein in formula made from cow milk. This study examined the rheological and structural characteristics of casein coagulum from ruminant milks under infant gastric digestion conditions.

Methods: Reconstituted milk powders (cow milk, n=5 and goat milk, n=10) were acidified to pH~4, at 37°C, modelling infant gastric conditions. The characteristics of the casein gel formed were measured over 3 h. The stiffness or strength of the casein gel was assessed by continuous measurement of the elastic modulus. The stress-point at which the casein gel was disrupted was also measured after 3 h. Whey-adapted infant formula, where the casein:whey ratio has been modified by the addition of whey, was also modelled in the study, by addition of various amounts of whey protein concentrate to cow or goat milk.

Results: Casein in cow milk coagulated at a slightly higher pH (pH 4.6) compared to casein from goat milk (pH 4.1). The strength or stiffness of the goat milk casein gel was 25-30% of that of cow milk (65 ± 26, goat; 209 ± 44, cow). The stress force required to break the casein gel from goat milk was 49% of that required to break the cow milk gel. Altering the casein:whey ratio by addition of whey to cow milk reduced the gel strength 14 fold. However, whey addition to goat milk had less influence on the gel strength of goat milk. This same difference is also reflected in formulas made from cow and goat milk.

Conclusion: The gel formed from casein in goat milk or from formulas made with goat milk was considerably softer and had a lower breaking stress than the casein gel in cow milk or cow milk formula. Whey addition was effective in reducing hardness of casein curd from cow milk. Caseins from goat milk required a lower pH to form a gel than cow milk, which is higher than the normal gastric conditions of infants (Mitchell et al 2001 Arch Dis Child 84, 273). Thus, it is probable that caseins from goat milk based formula are never fully coagulated within an infant's stomach. Future research will determine how the aggregation states of caseins from different milks within the stomach might impact on digestive behaviour in vivo.

Disclosure of interest: Prosser and Carpenter are employees of Dairy Goat Co-operative (N.Z.) Ltd, New Zealand who funded the study.

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NUTRITION - Basic science

N-P-016

Milk fat globule membrane (MFGM) protects against the development of necrotizing enterocolitis (NEC) in a neonatal rat model

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Objectives and Study: Necrotizing enterocolitis (NEC) is a severe inflammatory disease that affects the gastrointestinal tract of the premature infant and that causes significant morbidity and mortality. Recently, Milk fat globule membrane (MFGM) has gained considerable attention due to its nutritional and health benefits, more and more studies suggested that supplementation of MFGM in formula is safe and indicated positive effects. However, the effect of MFGM on NEC remains unclear. The aim of this study was to evaluate the effect of MFGM on neonatal rats with NEC.

Methods: Sixty-two newborn Sprague-Dawley rats (6~7g, 2 days old) were randomly divided into four experimental groups: Control (n=12, breastfed), NEC (n=20, underwent hypoxia, cold stimulation and formula gavage over four days), NEC+6g/L MFGM (n=15, 6g/L MFGM supplementation in formula), NEC+12g/L MFGM (n=15, 12g/L MFGM supplementation in formula). The general state, body weight, intestinal morphology, histological score, survival time, oxidative stress, and mucosal integrity were assessed. Enterocyte proliferation/apoptosis was evaluated by nuclear-associated antigen (Ki-67)/TUNEL. Meanwhile, the expressions of TLR4/MyD88/NF-kappaB pathway molecules in intestinal tissue and IEC-6 enterocytes were also analyzed by immunofluorescence, Western blot, and qRT-PCR.

Results: The activity and body weight of rats in NEC group were decreased, having abdominal distension and diarrhea with yellow green grume and bloody stool. Although the status of rats in 6g/L MFGM supplementation groups were similar to that in NEC group, rats in 12g/L MFGM supplementation group maintained the body weight, reduced the incidence of NEC from 85% (17/20) to 53.33% (8/15), increased the survival rate from 30% (6/20) to 66.67% (10/15), and attenuated the severity of bowel damage as compared to the NEC group. The expression of tight-junction proteins (ZO-1) was increased in the NEC rats treated with 12g/L MFGM. In addition, 12g/L MFGM supplementation down-regulated the concentration of malondialdehyde (MDA) and up-regulated the activity of superoxide dismutase (SOD), reduced enterocyte apoptosis and increased enterocyte proliferation. Furthermore, Western blotting demonstrated that MFGM substantially inhibited the TLR4, MyD88, NF-κBp65, p-NF-κBp65 protein levels and inhibited the mRNA expressions of proinflammatory mediators (IL-6, IL-1β, tumor necrosis factor-α) in the intestinal tissue and IEC-6 enterocytes.

Conclusion: Our results suggested that MFGM has beneficial effects on neonatal rats with NEC by attenuating oxidative stress, preserving mucosal integrity and suppressing inflammation via TLR4/MyD88/NF-kappaB pathway.
Maternal pre-pregnancy obesity alters term placental microRNA expression

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Objectives and Study: The placenta plays an essential regulator role in the maternal-fetal metabolism with the production of the widest array of molecules of any other organ except the brain. Obesity during pregnancy is associated to an increase of metabolic disorders, which contribute to create an unfavorable in utero environment through an aberrant placental development. First studies are demonstrating altered placental gene expression profile in obese women, and clearly more understanding of the molecular regulation in placenta from obese women is needed. We hypothesized that maternal obesity can alter placental microRNA profiles, and consequently, placental gene expression.

Method: RNA was isolated from term placentas of obese (n=5) and normal weight women (n=5). Placental microRNA profiles were analyzed using Affymetrix microarray platform. The microRNA expression profiles were determined by comparing the obese and normo weight groups (2 by 2 comparisons) by means of the rank product non-parametric test in the Bioconductor RankProd package.

Results: The PCA and hierarchical clustering analyses demonstrated clear distinction between placental miRNA expression profiles between obese and normoweight women, where the two study groups clustered into two distinct groups. 27 miRNAs showed different expression between groups. 7 miRNAs were up-regulated while 20 miRNAs were down-regulated in placentas from obese pregnant women.

Conclusion: Maternal pre-pregnancy obesity influences placental microRNA expression. The altered microRNA profile found in obese pregnant women may compromise maternal gene expression levels playing an important role in pregnancy-related processes and fetal growth and development, with unknown long-term consequences.

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Maternal body mass index, diet and mode of delivery shape the neonatal microbiota at birth

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Objectives and Study: An adequate nutritional and microbial environment during the perinatal period is key in promoting and supporting human health. Emerging evidence suggests that microbial contact begins already in utero. Maternal microbiota forms the main microbial source for neonatal microbiome although perinatal factors affecting the mother-neonate microbial transference are still under debate. It has been suggested that shifts in maternal microbial signatures would be transferred to their offerings and they would play a role during foetal development and have an impact the microbial colonization after birth. Our aim was to characterize the impact of different perinatal parameters such as maternal diet, body mass index (BMI) as well as mode of delivery on meconium microbiome at birth time.

Method: Meconium (n=94) samples were collected at birth and microbiome composition was assessed by 16S rRNA gene sequencing with the Illumina system. Data related to maternal BMI, weight gain during pregnancy, mode of delivery and neonatal birth weight and length were collected. Dietary records were collected by FFQ and intakes were converted to nutrients levels using National Food Composition Tables (CESNID).

Results: Maternal BMI, diet and mode of delivery had an impact on the meconium microbiota. Significant lower abundance of Bacteroidetes phylum and Bacteroides genus were observed in meconium from C-section compared to those observed in vaginal deliveries. Indeed, significant lower abundance of Bacteroides genus was associated to higher maternal pre-pregnancy BMI. No differences on microbial diversity and richness were found in the meconium microbiota. Maternal diet had an important influence on meconium microbiota. Hence, higher abundance of Bifidobacterium genus was related to higher maternal protein intake (p< 0.001, R=0.46) and vitamins such as vitamin A (p=0.037, R=0.29), Riboflavin (p=0.001, R=0.40), Niacin (p=0.004, R=0.37) or vitamin B6 (p=0.04, R=0.27) intake. Lachnospiracea (p=0.02, R=-0.3) and Ruminococcaceae species (p=0.05, R=-0.26) showed a negative correlation with proteins from vegetable source. Indeed, species from these families are positively correlated with saturated fatty acids intake (p< 0.05).

Conclusion: Meconium microbiota upon delivery is affected by the mode of delivery and other parameters, including the maternal pre-pregnancy BMI and diet. Our study suggests these prenatal and perinatal factors are influencing neonatal microbiota and may have an influence on the microbial colonization of the neonate and thereafter upon the immunological and metabolic programming with short- and long-term consequences on infant's health and development.

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The effect of weaning age on rat's small intestine

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Objectives and Study: Weaning of mammal progeny is associated with a change in food composition and mother offspring bonding separation. Weaning results in a critical period of low voluntary feed intake, during which the animal is adapting to the starter diet. The aim of the study was to evaluate effects of weaning age on early and late morphological changes that occur in a rat's intestine.

Method: we assessed intestinal histomorphometry and animals' growth in 21 days old pups and 90 days old mature animals that had been weaned early (d16), normally (d21) or late (d26).

Results: Early weaning resulted on day 21 in deeper crypts, lower villous/crypt ratio and smaller villous area. Crown-tail length correlated positively with the crypt depth and negatively with villous/crypt ratio. At age 90 days, crypts were shallower, the villous/crypt ratio was greater, and the villous area was smaller. Rats' crown-tail length correlated negatively with the crypt depth and positively with villous/crypt ratio.

Conclusion: Animals that are weaned early present different villi morphology based on the phase: acute phase villi and crypts are smaller impacting on food absorption, and leading to longer/thinner animals compared to late weaning. The chronic phase is a phase of compensation: villi and crypts are larger leading to larger animals compared to normal/late weaning.

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Anthropometric indices change rate in children with obesity risk polymorphisms rs9939609 of FTO gene and rs4994 of ADRB3 gene from birth to 4 years

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Objectives and Study: The growth of childhood obesity is of great concern. An increased rate of growth at an early age may be one of the reasons. Genetic factors play an important role in the development of obesity, but studies of their effect on growth rate in childhood are currently limited. The aim was to evaluate the influence of the genetic polymorphisms rs9939609 of the FTO gene and rs4994 of the ADRB3 gene on the growth rate of children.

Method: The anthropometric indices were studied in 47 conditionally healthy children observed in the outpatient clinics in the city of Smolensk (Russia) from birth to 4 years of age. Parents of children gave informed consent for research. We analyzed the children’s medical cards anthropometric data, followed by the calculation of Z-scores weight for age (WAZ), length/height for age (LHAZ), weight for length/height (WLHZ) and BMI for age (BAZ) (ANTHRO, 2005) at birth and their changes (delta) from 0 to 1, 2, 3, 6, 12, 24, 36, 48 months. At the age of 4, the thickness of 5 skin folds was measured by the method of caliperometry: above the triceps, biceps, under the angle of the scapula, above the crest of the ilium, and at the hip. Children were genotyped by the polymorphisms rs9939609 and rs4994 using DNA isolation from buccal epithelium followed by real time PCR. Results were analyzed by the SPSS 20. The differences were considered statistically significant at p<0.05.

Results: The genotype TT of rs9939609 polymorphism was detected in 25.5%, AT in 61.7%, AA in 12.8% of children. The genotype TT of rs4994 polymorphism had 80.9%, the genotype of CT - 19.1% of children, the CC genotype was not revealed. At the time of birth the examined children did not have significant differences in the anthropometric parameters, depending on the genotype of the polymorphisms studied. Carriers of genotype AA of rs9939609 polymorphism demonstrated accelerated growth as they had higher values of delta WAZ, WLHZ and BAZ at all periods studied. There were no significant changes in the delta LHAZ. Carriers of genotype CT of rs4994 polymorphism also showed a higher rate of change in WLHZ and BAZ but reduced change of LHAZ compared to TT genotype carriers during all periods studied. Since the delta WAZ did not undergo significant changes depending on the genotype, the increased change in WLHZ and BAZ in carriers of CT genotype was apparently due to a decrease in the growth rate of children in length. At the age of 4 carriers of the AA genotype of rs9939609 polymorphism had higher BAZ and thickness of skin folds above the crest of the ilium (11.3 ± 0.8 cm vs. 8.5 ± 0.8 cm, p =0.031), and at the hip (21.2 ± 1.1 cm vs. 14.9 ± 1.1 cm, p = 0.047) as compared to carriers of the TT genotype. The average BAZ and the thickness of skin folds in carriers of the TT and CT genotypes of the rs4994 polymorphism did not differ significantly.

Conclusion: Both the carriers of AA genotype of rs9939609 polymorphism and the CT genotype of rs4994 polymorphism are characterized by an increased change in the WLHZ and BAZ. However, the former seem to have a greater risk of developing obesity at young age than the latter, and the predictive value of accelerated change of these indicators is different for the 2 polymorphisms studied.
Factors influencing the quality and quantity of human breast milk - Is there a need to standardize sampling of milk for characterization of lipids and lipophiles?

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Introduction: The composition of human breast milk (BM) is dynamic and is reported to vary based on maternal and infant factors, presumably to reflect nutritional needs of growing infants. Additionally, literature suggests that methodological aspects such as BM sampling, storage and analyses for research may also influence the quantification of certain nutrients such as lipids and lipophiles, and therefore must be carefully considered at the study design and execution stages. In order to gain insight into the nutritional needs and/or intake of the breastfed infants, and understand how it is influenced by maternal and infant factors, it is imperative that we eliminate the variability encumbered by these methodological aspects. Therefore, in this paper we holistically reviewed the impact of maternal factors (anthropometry, socio-demographic characteristics, obstetric history, physical health, mental health, medications, drugs, lifestyle and dietary habits), infant factors (gestational age at birth, anthropometry, gender, breastfeeding frequency and duration, and their overall physical health), and methodological aspects of study that may impact the quality and/or quantity of BM and eventually the quality of study results and conclusions. Additionally, we emphasize the need for standardization of BM sampling to characterize nutrients that are known to be affected by the study methodology, as well as nutrients for which the effect has not yet been researched or clearly demonstrated.

Methodology: We searched SCOPUS database with predefined keywords for all scientific literature related to factors that are known to influence or could potentially influence BM quality and quantity across lactation.

Results: We summarized the review findings into the following categories, according to the impact each of these factors have on BM quality and quantity:

1. Low to minimal impact - infant suckling duration, maternal moderate physical activity, social factors, and stress.
2. Factors that have an impact and must be recorded to facilitate appropriate interpretation of data) - maternal diet, anthropometry, lifestyle (smoking, alcohol/caffeine consumption, severe physical activity), feeding frequency, obstetric history (e.g. parity, mode of delivery), infant birth weight, gender, stage of lactation, maternal demographics.
3. Factors that could impact the quality of study results and therefore must be standardized - time and type of BM sampling, treatment of samples post collection, temperature and length of BM storage until analyses, handling and transport of samples to another laboratory, freeze-thaw cycle and analytical procedures.

Conclusion: Current evidence suggests that numerous maternal, infant and study methodological aspects have an impact on BM quality and quantity. In order to eliminate or minimize the bias caused by these methodological factors, ensure comparability across studies and facilitate the accurate interpretation of study results, it is critical to standardize the methodology at the study onset and appropriately consider all relevant factors at the data analyses stage. Our review suggests that the most affected nutrients were either lipids or liposoluble nutrients, which implies a need to standardize BM sampling for their characterization.

Disclosure of interest: All authors are employees of Nestec Ltd.

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Milk fat globule membranes support intestinal barrier integrity and function in a rat model for short bowel syndrome

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Objectives and Study: The milk fat globule membrane (MFGM) contains bioactive phospholipids, gangliosides and glycoproteins, which have been shown to inhibit pathogen colonization and maintain gut barrier integrity individually. The aim of the present study was to evaluate the protective effects of MFGM on intestinal barrier integrity and function and the possible underlying mechanism through NLRP3 inflammasome pathway modulation in a rat model of short bowel syndrome.

Method: The milk fat globule membrane (MFGM) contains bioactive phospholipids, gangliosides and glycoproteins, which have been shown to inhibit pathogen colonization and maintain gut barrier integrity individually. The aim of the present study was to evaluate the protective effects of MFGM on intestinal barrier integrity and function and the possible underlying mechanism through NLRP3 inflammasome pathway modulation in a rat model of short bowel syndrome.

Results: Sham operated animals had higher body weight than SBS and SBS+MFGM groups, and the latter two groups showed similar results in body weight, villus height and crypt depth of ileum. Intestinal permeability and BT rate were increased in the SBS group as compared with Sham and SBS+MFGM groups (p &LT; 0.05). MFGM supplementation also resulted in higher expressions of the tight junction proteins claudin 1, claudin 2 and occludin in ileum than SBS group. The ileum tissue of SBS rats showed higher IL-1β levels than Sham and SBS+MFGM group (P &LT; 0.05), and IL-18 levels in ileum tissue were significantly lower in SBS group compared with Sham and SBS+MFGM groups (P &LT; 0.05). SBS+MFGM group also showed significantly higher sIgA concentration in ileum contents than those in SBS and Sham groups. SBS rats had significantly higher expressions of NLRP3, ASC, caspase-1 in ileum tissues, with no difference detected between Sham and SBS+MFGM group.

Conclusion: Enteral supplementation of MFGM helped to maintain intestinal barrier integrity & function and reduce NLRP3 inflammasome activation in SBS. Overall, these observations support a role for MFGM in gut health and provide experimental support for applications in intestinal failure although further clinical and mechanistic studies are needed.

Disclosure of interest: YZ and TTL are employees of Mead Johnson Nutrition

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Does impaired P-glycoprotein efflux function facilitate the early translocation of lipopolysaccharide in the setting of total parenteral nutrition?

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Objectives and Study: Lipopolysaccharide (LPS)-induced inflammatory strike is a major mechanism responsible for the pathogenesis of intestinal barrier dysfunction in the setting of total parenteral nutrition (TPN). However, it is still unclear how, during the early stage of TPN, LPS translocates across the epithelium and triggers the inflammatory responses. Our previous studies have demonstrated that intestinal P-glycoprotein (P-gp)-mediated efflux function serves as a natural defense system against the translocation of LPS in vitro, herein we hypothesize that the impaired P-gp function may be a novel risk factor that facilitates the early translocation of LPS and triggers the inflammatory responses in vivo.

Method: Five-week-old SD male rats were given TPN or enteral chow for 3-7 days, and the rats were sacrificed on the 3rd and 7th day after TPN surgery. The expression of intestinal P-gp was examined by western blot and immunohistochemistry, and the levels of inflammatory cytokines including TNF-α, IFN-γ, IL-1β and IL-6 were examined by Q-PCR. P-gp-mediated efflux function was evaluated by the absorption of rhodamine 123, and the epithelial barrier function was simultaneously evaluated by examining the permeability of TRICT-dextran. LPS translocation was examined by two independent methods, including an in situ assessment using a LPS-ELISA kit and a real-time assessment using FITC-labeled LPS. Briefly, the in situ assessment was evaluated using 1 mg of mucosal content isolated from the ileum, and the content of LPS was determined using an ELISA kit. The real-time assessment was evaluated by the translocation of fluorescent LPS after administration of 100 ug FITC-LPS into the ligated ileal loops, and the content of FITC-LPS within the mucosa was determined using a spectrophotometry.

Results: Western blot analysis and immunohistochemistry staining suggested that the expression of intestinal p-gp was decreased by approximately 50% in the ileum of the rats receiving 3-day TPN administration. Consistently, the portal concentrations of rhodamine 123 in the sham rats and the 3-day-TPN rats were 46±14 and 88±9 (ng/ml), respectively (p<0.05), while the levels of TRICT-dextran in these two groups were 2.2±0.6 and 2.6±0.4 (μg/ml), respectively (p>0.05). These results indicated that 3-day-TPN is suitable for studying the role of P-gp in the translocation of LPS, without the potential impact of impaired barrier function. No obvious alterations in the expression of cytokines were observed in the 3-day TPN. Consistently, no significant differences in the in situ LPS content were observed between sham and 3-day TPN group: 4.3±1.2 and 4.7±2.6 (eU/mg protein) in the sham and TPN group, respectively (p>0.05). Importantly, however, the permeability of FITC-LPS was significantly increased upon 3-day TPN treatment. The contents of mucosal FITC-LPS were 5.1±2.8 and 12.6±4.9 (ng/mg protein) in the sham group and 3-day-TPN group, respectively (p<0.05), indicating a significant intracellular accumulation of FITC-LPS due to the down-regulation of P-gp.

Conclusion: Down-regulation of P-gp occurs ahead of the impairment of epithelial barrier function. In the early stage of TPN, the impaired P-gp efflux function may facilitate the early translocation of LPS and trigger the subsequent inflammatory responses.
Metabolic bone disease in children with intestinal failure is not associated to parenteral nutrition (PN) dependency index

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Objectives and Study: Children on long-term home PN are at increased risk of metabolic bone disease (MBD) including 25-hydroxyvitamin D3 (25-OH D3) deficiency, suboptimal growth and decreased bone mineral density (BMD). PN dependency index is defined as the ratio of non-protein energy intake (NPEI) provided by PN over the resting energy expenditure (REE) calculated using the Schofield equations. Children with PN dependency index above 1.2 are considered to be highly dependent on PN. The factors associated with MBD are not well known.

Method: Children above the age of 5y and receiving PN for more than 2y were included. Blood and urine analyses and dual X-ray absorptiometry (DXA) were performed and correlated to PN dependency index. The DXA machine used was Hologic QDR-4500W fan-beam scanner (software version 12.6.1, Hologic Inc., Bedford, USA).

Results: Forty children were assessed at 12.4±4.5y of age. Mean age at PN start was 1.1±3.6y. The indications for PN were short bowel syndrome (SBS, n=21), chronic intestinal pseudo-obstruction syndrome (CIPOS, n=10) and congenital enteropathies (CE, n=9). The mean number of weekly PN perforusions was 6±1. The calcium and phosphorus intakes from PN were 0.4±0.1 and 0.6±0.3mmol/L respectively. The mean concentrations of calcium and phosphorus in serum were 2.3±0.1 and 1.4±0.3mmol/L respectively. All children had normal creatinin in serum and none had signs of nephrocalcinosis on ultrasound. The mean serum level of 25-OH3 was 26.5±9.1ng/mL (normal: 30-60) and parathyroid hormone (PTH) was 39.3±18.6ng/L (normal: 10-55ng/L). Eight children (20%) had PTH levels above normal with low 25-OHD3 levels. Only 16 children (40%) had a normal value of 25-OHD3. The mean weight and height Z-scores SDS were 0.4±0.9 and -0.5±1.1 respectively. The actual height was lower than targeted height (p< 0.001). The BMD Z-scores, adjusted to the 50th percentile of height, of the spine, the left femur and the whole body were -1.1±1.7, -1.2±1.5 and -1.5±1.8 SDS respectively. Children with CE had significantly lower BMD values than those with SBS and CIPOS. Only two children had bone fractures after a mild trauma (5%). The PN dependency index was 1.1±0.3. High PN dependency (NPEI/REE >1.2) did not increase the risk of MBD.

Conclusion: All children on long-term PN, and particularly those with CE, are at risk of 25-OHD3 deficiency, suboptimal growth and osteopenia. PN-related bone fractures are rare. The degree of PN dependency does not increase the severity of MBD. Close follow-up remains mandatory.

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The effect of Modulen IBD in the treatment of inflammatory bowel disease

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Objectives and Study: Nutritional support in addition to the various anti-inflammatory drugs used in the treatment of inflammatory bowel disease (IBD), especially in cases with malnutrition and lack of appetite, is thought to positively affect these patients’ entry into remission. This study investigated the effect on clinical and laboratory values of Modulen IBD nutrition support in addition to treatment in cases of IBD.

Method: 73 cases of IBD monitored between January 2012 and January 2016 at the Cukurova University Faculty of Medicine and the Necmettin Erbakan University Faculty of Medicine pediatric gastroenterology departments were evaluated retrospectively. Cases were classified as Crohn’s disease either receiving (CD-M; n=16) or not receiving Modulen (CH; n=19) and subjects with ulcerative colitis either receiving (UC-M; n=13) or not receiving Modulen (UC; n=25). Modulen was added to diets in the form of 1000 cal/day in addition to IBD treatment.

Results: No statistically significant difference was observed between the CD-M and CD groups in terms of laboratory values or CDAI scores during monitoring. CDAI scores and sedimentation values in both groups were significantly lower after 1 week compared to at time of diagnosis and remained low throughout the study. CRP values in both groups were significantly low after the 3rd month, although IgG levels only decreased significantly compared to at time of diagnosis in the CD-M group at the 6th month. UCAI was significantly lower after the 1st week compared to at time of diagnosis in the UC-M and UC groups. CRP was lower at the 6th month compared to at time of diagnosis in both groups. UCAI score was significantly better in the UC-M group as of the 3rd month compared to the UC group.

Conclusion: Earlier clinical and laboratory improvement was observed in cases of CD and UC with Modulen support.

Keywords: inflammatory bowel disease, modulen, children, nutrition

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Nutritional assessment of children with Down syndrome with and without associated congenital heart defects

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Objectives: Children with Down syndrome (DS) are prone to feeding difficulties, congenital heart defects (CHDs) and defective energy intake though they are often overweight when compared to contemporaries. This study was designed to evaluate the nutritional status of Down syndrome children with and without associated CHD.

Methods: This study included 80 patients with DS recruited from the Genetic and Pediatric Cardiology Clinics at Children Hospital, Ain Shams University. Patients were classified into two groups according to presence (group I) or absence (group II) of CHD. Dietetic history was taken using 24 hour dietary recall and food frequency questionnaire. Data was analyzed into macro- and micro-nutrients and referred to as a percentage from the recommended daily allowance (RDA). Anthropometric measurements were interpreted using Z scores.

Results: Malnutrition, stunting and wasting were detected in 23.8%, 45% and 11.3% of patients respectively. Their prevalence rates were significantly higher among group I (34.2%, 55.3% and 21.1%) when compared to group II (14.3%, 35.7% and 2.4%) respectively (p<0.05). Group I had statistically significant lower mean values of daily intake of energy (543.2 ± 194.14 K cal), carbohydrates(69.28 ± 29.91 gm), fat(20.06 ± 8.44 gm) and proteins(21.41± 9.00) when compared to group II (821.82 ± 299.94 K cal),(97.82± 41.98 gm),(33.94±13.53 gm) and (31.27±15.98 gm) respectively(p<0.05). Group I had statistically significant lower mean values of daily intake of iron, calcium, sodium, potassium, phosphorous, selenium, vitamin B1 and vitamin D when compared to group II(p<0.05).

Conclusion: Children with DS associated with CHD are more prone to nutritional complications. Nutritional rehabilitation strategy including multiple micro-nutrient supplementation is crucial in the management of those children with early involvement of dietitians and caregivers.

Keywords: Recommended daily allowance; Down syndrome; congenital heart disease; Z scores; malnutrition.

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Who is your dietitian? Diet of breastfeeding mothers with an allergic infant lacks many essential nutrients

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Objectives and Study: Prevalence of food allergy is increasing. Food elimination is an effective treatment option for the breastfeeding mother. However this strategy is not without potential risks. Dietitian supervision is necessary for the dieting mother. This study is performed to determine the dietitian referral rates, diet content, and the effect of dietitian advice in breastfeeding mothers on an elimination diet.

Method: Study is performed in paediatric gastroenterology outpatient clinic. Three separate groups were created; study group 1 consists of mothers who were already on an elimination diet, study group 2 consists of mothers who were about to start diet, and control group consists of mothers who aren't on a diet. Diet content is calculated from 3 day dietary records (3-DDR), two times for group 1 (before and after dietitian advice), one time for group 2 (after dietitian advice) and 3 (at the admission). Dietary content analysis was made by Nutrition Information System program (BeBiS) V7.0 specially developed for Turkey. Anthropometric measurements (weight, height, BMI) and handgrip strength of the mothers were determined at the first admission. Edinburgh Postpartum Depression Scale was administered to every mother. Demographic data was collected by a standard form.

Results: 125 mothers were included in the study. However 25 of them were excluded (20 didn't return 3-DDR, 2 carpal tunnel syndrome, 2 already on a weight loss diet, and 1 baby died). There were 41, 12, and 47 mothers in three study groups. In group 1, 24.4% of mothers had started elimination diet by themselves without consulting a physician. Milk consumption during pregnancy was significantly higher in the control group. Postpartum depression score was significantly higher in group 1 (12.1±4.9 vs. 7.08±, and 8.0±4.8 for group 1, 2, and 3 respectively, p<0.001). Anthropometric measurements and handgrip strength were similar. Mean diet duration was 1.4±1.0 month for group 1. None of the group 1 mothers were consulted to dietitian before starting the diet. Food label reading education was given to 25.5%. Most 36% of the mothers were taking additional calcium+ vitamin D supplements. Most frequently eliminated food was milk (98%), egg (76%), meat (46%), soy (32%), chicken (29%), and fish (10%). Significant benefits were observed in only 51% (37% very much, 24% some benefit) of the babies after elimination diet. Daily intake of calories (1253±242 kcal, 1710±334 kcal, and 1687±286 kcal, for groups 1, 2, and 3 respectively, p<0.001), proteins and many other nutrients except vitamin A, D, B12, and water were significantly lower in group 1. After dietitian consultation, daily intake of calories (1253±242 kcal vs.1612±349 kcal), protein and all nutrients except vitamin B12, niacin, cholesterol, vitamin D, and fluorine were increased significantly in group 1 and were similar to group 2, and group 3.

Conclusion: Elimination diet carries significant nutritional deficiency and depression risks for the breastfeeding mothers who weren’t counselled to dietitian. Short and long term effects of dietitian advice on mother’s nutritional status, breastfeeding success, and growth of the infant must be determined.

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Parents evaluation of an MDT complex enteral feeding clinic

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Objectives and Study: Children with severe disability have an array of complex gastrointestinal problems including: gastroesophageal reflux, foregut dysmotility and airway safety, often these problems overlap. Decision making for these patients requires multiple health professionals, and can involve medical therapies, surgical intervention and/or jejunal feeding. The MDT Complex Enteral Feeding (CEN) Service was established in our centre in 2013. Its aspiration was for patients to see all relevant health professionals in a single visit to streamline the delivery of complex decisions eg further medical therapy; insertion of PEG; fundoplication; jejunal feeding, and to manage all jejunally fed patients under a nurse-led service. As part of the ongoing care needs for our patients and families, it was important to determine if the service was meeting the needs of the child/young person and their families.

Methods: CEN clinics have been formally running since 2013, using our database and electronic patient record system data was collected of all patients who were seen within our service. A questionnaire was designed and this was sent to all families who supplied an email address. The questionnaire was designed using survey monkey and a link was sent to the families as part of a covering email. A reminder email was sent 2 weeks following the initial request.

Results: 84 patients were identified as coming through the CEN clinic/MDT inpatient service since 2013, 6 were excluded as they had passed away. 38 families (49%) had shared their email addresses and were sent a questionnaire. 23 (60%) returned the questionnaire. 17 (77%) were seen in a CEN clinic, 4 (18%) were seen as inpatients and 1 (4.5%) responded that they did not know if their child had been seen. 18 families (42%) felt that the appointment was helpful/very helpful, with 1 family (4.5%) feeling it was of no value. 22 (100%) of families were seen by a Gastroenterology consultant and Complex Enteral Nutrition Clinical nurse specialist, 15 (68%) were seen with a surgeon, and only 12 families (54%) seen by a dietitian. 21 families (95%) felt that they were listened to during their appointment, and 16 families (73%) felt that the 30 min appointment was enough time. When asked if the family had a clear plan on leaving clinic, 17 (77%) answered yes, and 5 (22.8%) answered no. When asked to score the service from 1(lowest) to 10 (highest), the weighed average was 7.52/10, with 7 (30%) scoring 10/10. Comments received included there should be shorter waiting times, sending information leaflets prior to clinic appointment, better co-ordination with teams in other hospitals. When asked how the service could be improved, 10 families (55%) asked for information leaflets, 8 families (44%) asked for youtube videos/video links, 8 families (44%) would like a webpage and 7 families (39%) asked for a mobile phone app.

Conclusions: The results of this audit have been very promising, it is clear that the CEN service has played a key role in the delivery of care to a number of children/young people and their families within our centre. Service developments will include increased written information and potential use of online resources.

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Nutritional status in hospitalized children with Hirschsprung's disease

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Objectives and Study: Malnutrition in hospitalized children is a serious problem of paediatrics. According to the literature, the incidence of undernutrition in hospitalized children can range from 6.1 to 54% in different regions of the world. This problem is especially significant for patients with pathology of the gastrointestinal tract, requiring surgical intervention.

Method: In 76 children (46 boys) with Hirschsprung disease (HD) at age from 2 months to 16 years a cross-sectional study was performed. The survey included a malnutrition risk screening (STAMP tool), anthropometric data (height, weight) assessment through the calculation of Z-scores with the support of the WHO Anthro, 2006 software (for children under five years) and the WHO Anthroplus, 2009 software (for children older than five years), laboratory evaluation (serum total protein and albumin concentration), dietary intake assessment via 24-hour diet recalls and "1C Nutrition" computer program. The malnutrition was diagnosed based on WHO and ICD-10 criteria. In 21 patients over 5 years, bioelectrical impedance analysis (BIA) was performed, employing a "ABC-02 MEDASS" device.

Results: A high risk of malnutrition was observed in 49 (64.5%) patients, a moderate risk in 27 (35.5%). Undernutrition was detected in 41 patients (53.9%) - moderate in 7 (17%) and severe in 4 (10%) patients. Total blood protein was reduced in 26 patients with undernutrition (63%) and in 5 (14%) children without undernutrition (p = 0.068), albumin was reduced in 15 patients with undernutrition (37%) and in 1 child (3%) without undernutrition (p = 0.000). According to BIA, BMI was below average for an age in 12 (57.1%) children. At the same time, total body fat remained within normal limits in 18 (85.7%) children, in 3 (14.3%) it was above the norm; lean body mass, active cell mass and musculoskeletal mass were reduced in 9 (42.9%) children. An average protein intake in children with undernutrition was reduced by 15%, fat - by 35.8%, carbohydrates - by 31.5%, the overall energy value of the diet was reduced by 25%. There was revealed a lack of some micronutrients: calcium was decreased by 45%, vitamin B - by 65%, thiamine - by 38%, vitamin C - by 34%, iron - by 31.4%.

Conclusion: There is a high- moderate risk of undernutrition development in all children with Hirschsprung disease, being admitted to the surgical department for surgical treatment. Complex assessment of nutritional status, including different malnutrition indicators and dietary intake assessment should be applied in children with colonic agangliosis at admission to hospital for the timely organization of adequate nutritional support.

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Anthropometric findings and nutritional properties in children with functional constipation

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Objectives and Study: Functional constipation (FC) is a common problem of childhood. This study was intended to investigate the nutritional properties and anthropometric findings in children with FC.

Methods: In this prospective study, 1-18 years old 80 children (40 with FC patients and 40 healthy controls without FC) admitted to pediatric gastroenterology outpatient clinic were included. FC patients were defined according to the Rome IV diagnostic criteria. Parents gave written informed consent and all children provided assent to participate. Patients' clinical and demographic data was determined. Anthropometric measurements of weight, height, and body mass index (BMI) were obtained. BMI z-scores between +1 and +2 were considered as overweight, and above +2 as obesity. Malnutrition was defined according to Waterlow criteria. The control group included children who were not diagnosed with FC or other organic disease. The healthy controls were matched with FC patients for age and gender. They were within normal limits of weight and height according to age. The three-day diary of FC patients and healthy controls was assessed by the same nutritionist and the daily average calory, daily average fiber, protein and fat content were calculated.

Results: Average age of FC patients was 7.93 ± 4.46 years and average age of the healthy controls was 8.13 ± 4.5 years. There is no difference for age and gender between groups. Twenty-one patients with FC (52.5%) were male. Average onset age of constipation was 4.45 ± 4.2 years. Average duration of constipation was detected 41.9 ± 46.9 months, and average stool frequency was detected 2.7 ± 1.4 weeks. Painful defecation (87.5%), large diameter stool story (85%), abdominal pain (77.5%) and abdominal distension (65%) were the most common complaints in FC patients. Constipation family history was detected 47.5% of FC patients. Three patients were obese and one patient was overweight in FC patients. Loss of appetite was noted in 24 (60%) of FC patients. Malnutrition was found in 12 (30%) of these patients, acute malnutrition in 9 patients, chronic malnutrition in 1 patient, and acute on chronic malnutrition in 2 patients. Twenty-four (60%) patients with FC were normal height and weight according to their age. There was a significant difference between the patients with FC and healthy controls in terms of the average daily protein intake (p=0.02). There was no significant difference between groups in terms of average daily carbohydrate, fat, fiber amount and daily average calory intake.

Conclusion: Most children with FC were found to have normal height and weight in terms of age. Average daily protein intake in FC children was significantly lower than in healthy controls. However, a further large studies is needed about correlation between nutritional contents and FC.

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NUTRITION - Clinical nutrition

N-P-031

Metabolic stress during the daily discontinuation of cyclic given total parenteral nutrition (TPN) in children with severe intestinal failure (IF)

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Objectives and Study: Even in children with chronic intestinal failure (IF) depending totally on parenteral nutrition (TPN) a discontinuation of parenteral nutrition (PN) for some hours during the day (cyclic TPN) is feasible. However, patients with severe IF due to short bowel syndrome (SBS), extensive malabsorption syndrome - with only minimal oral/enteral feeding - this daily 'parenteral nutrition free interval' (PNFI) might be a critical fasting period since their capacity to store nutrients and energy is limited. These children are on a higher risk to develop metabolic stress like hypoglycaemia, acidosis or dehydration during PNFI. There are no systematic investigations of the PNFI in terms of metabolic changes (MC) in paediatric patients. Aim of our study was to evaluate MCs during PNFI with intention to determine criteria allowing to estimate the tolerable duration of PNFI in IF patients unable to absorb relevant oral/enteral nutrition.

Methods: Retrospective study of PNFI measurements (in-house protocol: blood gas analysis, glucose, lactate, sodium, osmolarity, clinical dehydration score, weight - after disconnecting/before reconnecting TPN) in patients included in our Intestinal Rehabilitation Program (2009-2014). Analysis with respect to age, underlying diseases and an 'age-dependent critical PNFI duration', defined for Infant 0.5≤β yrs: 4h PNFI; Young Child 2≤6 yrs: 6h PNFI; Child 6≤12 yrs: 8h PNFI; Adolescent 12≤19 yrs: 12h PNFI; (WHO classification).

Results: Investigation of 102 PNFI measurements in 48 pts., 24 male, mean age 4.9 yrs. 38/48 pts. with SBS, mean residual small bowel length 23.5 cm, 47.9% without ileocecal valve. Mean PNFI duration was: Infant 6.5 ± 3.1 h, Young Child 8.75 ± 2.7 h, Child 11.5 ± 3.3 h, Adolescent 10.0 ± 2.1 h. Relevant metabolic changes (MC) in 42.6% of cases: e.g. acidosis 12.7%, alkalosis 23.4%, MC most frequent in group Child. Depending on PNFI duration pts. showed weight loss and a decline in lactate (n.s.). In pts. with PNFI above the critical duration (69.2%) we found a decrease of glucose in 25.5% (to critical levels in 11.8%) and a 2.2fold higher risk for dehydration. Pts. with renal insufficiency (8/48): significant decline of bicarbonate (p=0.02) and base excess (p=0.04), pH increase (p=0.03). Intestinal failure associated liver disease (IFALD) (28/48 pts.) and type of IF (SBS vs. functional IF) were not associated with MC. Children 6-12 yrs. old revealed the highest rate in MC (36.4%) and the most significant weight loss (mean 640g). None of documented MC led to clinically severe complications.

Conclusion: First detailed investigation of the 'parenteral nutrition free interval' (PNFI) showing that children with IF depending completely on PN without relevant intestinal caloric intake appear to have a high risk for metabolic changes during their PNFI especially if this is of longer duration. Patients with renal insufficiency and age 6-12 yrs. are more likely to experience metabolic stress while disconnected from PN. At least, choosing a PNFI duration below critical time limits (study definition) seems to be safe in terms of metabolic complications. Findings of this retrospective analysis should be validated prospectively. Our results may contribute to a safer calculation of the PNFI, especially in pts. without relevant oral/enteral nutrition.

Disclosure of interest: A. Busch declares that parts of the study were funded by Fresenius Kabi, Germany. A. Maute has no conflict of interest to disclose.

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UCP2 placental gene expression seems to have long-term effects on children neurodevelopment up to 6 years of age

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Objective and Study: Research indicates, children born to mothers who presented with obesity or diabetes during gestation have increased neurodevelopmental difficulties. UCP2 is a mitochondrial uncoupling protein responsible for lowering oxidative stress in cells by separating proton pumping from oxidative phosphorylation. It is widely expressed in the central nervous system, placenta and pancreas. UCP2 expression is usually upregulated during obesity and may have a significant role in determining infant neurodevelopment in the offspring of obese and gestational diabetic mothers. The study aims to uncover to what extent placental UCP2 expression is related to long-term infant neurodevelopment.

Methods: This is a prospective study, involving 113 children participating in the PREOBE Follow-up study. The children were subdivided into 4 groups, depending on their mothers’ metabolic condition during pregnancy: Normal weight (N;47), Overweight (Ov;27), Obese (Ob;12) or Gestational Diabetes (GDM;27). Infants’ neuropsychological development was assessed by the Bayley III test at 6 and 18 months, Cumanin test at 3.5 years and BENCH neuropsychological battery at 6 years of age. UCP2 expression was analyzed by RT-PCR. Statistical analysis, performed using SPSS version 24.0, ANOVA, MANCOVA and Chi square tests, were corrected by confounding factors: maternal age, gestational weight gain and smoking during pregnancy, and were adjusted by applying Bonferroni correction.

Results: UCP2 was up-regulated in overweight and obese women, but not by GDM. At 6 months of age, infants born to GDM mothers showed better language composite scores when UCP2 was down-regulated in the placenta (p_adj=0.039). When UCP2 expression was up-regulated in the placenta, at 18 months, babies born to Ov mothers had better scaled gross motor scores (p_adj=0.015), and children born to Ob mothers, at 3.5 years of age, showed better verbal development scores (Cumanin test) (p_adj=0.028). However, these effects disappeared at 6 years of age, when children born to Ob mothers showed a lower number of abstract reasoning hits related to UCP2 up-regulation in the placenta (p_adj=0.029).

Conclusion: Our results suggest that placental UCP2 expression may have a significant impact on neurodevelopment during foetal life, with long-term consequences. The mechanisms involved in the neurodevelopmental effects of UCP2 gene expression in the placenta, suggest an adaptive and protective placental response against oxidative stress with increased BMI. The relationship established between placental UCP2 gene expression and child neurodevelopment must be confirmed with further studies.

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Nutritional support in children with moderate to severe neurological diseases and self-efficacy for managing psychological symptoms in their caregivers

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Objectives: Many children with moderate-to-severe neurological diseases require long-term care including nutritional support. These circumstances have a special impact at personal, social and economic level for the family, affecting mainly the caregiver. Objectives of this study are: 1) to describe the clinical and anthropometric characteristics of neurological impaired children and 2) to analyze the burden and the influence of the disease on the family environment.

Methods: A prospective observational multicenter study was conducted in children with moderate-to-severe neurological impairment (equivalent to Gross Motor Function System Classification, GMFCS III-V). Data collected included: medical records, anthropometric measures (transformed into z-score for age and sex according to WHO references) and nutritional support. Caregivers answered the following questionnaires: Impact of Childhood Neurologic Disability Scale (ICND), Revised Scale for Caregiving Self-Efficacy (RSCSE), Parenting Stress Index-Short Form (PSI-SF), Brief Symptom Inventory (BSI) and Impact on Family Scale (IOFS) of caregivers of children with neurological diseases.

Results: A total of 35 caregivers (30 female, aged 35-49 years) were recruited. Children's mean of age was 9.4 years (SD 3.8). The most common diagnosis was cerebral palsy (23 children). All patients were nutritional assessed regularly. 26% of children received feeding by gastrostomy tube while the others required oral supplementations, mainly polymeric formulas as well as mineral and vitamins supplements. In 52% of children, the weight z-score was below 2SD; height z-score was below 2SD in 50% patients; and body mass index resulted below 2SD in 25% children, suggesting prevalence of chronic malnutrition. Caregivers presented high stress levels (PSI-SF=69.7), 46% of parents suffered anxiety (BSI=65.4) and/or depression (BSI=64.6) and they felt not much confident in asking a friend or family member to stay with the children (RSCSE= 49.5). The disease had an important impact (IOFS) at family (M=68.1), personal (M=61.8), economic (M=59.2) and social (M=48.8) levels. Applying ICND scale, the neurologic disability was the area with the strongest negative effect on the well-being of the family.

Conclusions: The predominant nutritional status of the children presenting moderate-to-severe neurological impairment was chronic malnutrition. The neurological disease had an important impact on the family environment, influencing negatively on the well-being of caregivers and conditioning remarkable burden at personal, social and economic family levels.

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Malnutrition in pediatrics: inpatient screening & follow-up on a general ward

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Objectives and Study: In this study we performed a malnutrition-screening of hospitalised children between 1 and 18 years at admission to a general paediatric ward of a tertiary care center with a follow-up seven days after admission/on day of discharge and four months after hospitalisation by phone. The aim of this study is to review the success of the clinical treatment focussing on existing or risk of malnutrition.

Methods: Measurements obtained included anthropometric measurements, a nutrition interview and an extended version of the Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP). The second measurement of weight was taken seven days after admission or on the day of discharge if this was minimum 3 days after admission. R Studio 3.4.2 was used for statistical analysis and diagnosing malnutrition by calculating height/length-for-age (HfAz)-, weight-for-age (WfAz)-, weight-for-height/length (WfHz)-, body mass index-for-age (BMIz) and mid-upper-arm circumference (MUACz)-z-scores with the childsds package with KIGGS and WHO for reference.

Results: The mean age of the 68 participants (male (m) = 38; female (f) = 30) was 8.68 (± 5.26) years. The main reasons for hospitalisation in the tertiary center were gastrointestinal diseases (29.41 %), diabetes mellitus (11.76 %) and rheumatic diseases (11.76 %). The mean WfAz at admission was -0.550 (± 1.640). Due to the mean duration of hospital stay of 2.5 (2.0 - 5.25) days and a minimum distance of three days between measurement one and two, only 25 inpatients were available for measurement two. The mean WfAz at measurement two was -0.554 (± 2.189). The WfAz was significantly lower at measurement two compared to measurement one (p = 0.035). At admission 29.41 % and at measurement two 24 % were malnourished. The longest median stay had the patients with serve malnutrition (4.0 (2.0 - 6.0) days). The included STAMP screening tool assigned 16.2% of inpatients to small risk, 47.1 % to moderate risk and 36.8 % to serve risk for malnutrition. The results of measurement three will be collected in December 2017 and January 2018 and added to the presentation.

Conclusion: A significant share of patients was malnourished at admission and the majority of patients lost weight during their hospital stay. The weight and height development follow-up will be interesting regarding to the evaluation of mid to long term consequences.

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NUTRITION - Clinical nutrition

N-P-035

e-Pinut 2017 - weight variation in hospitalized children

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Objectives and Study: Malnutrition increases the occurrence of complications and increases length of hospital stay (LOS). Weight loss during hospitalization, i.e. the constitution of malnutrition, is poorly documented in Paediatrics. The main objective was to analyze the occurrence of malnutrition according to LOS in hospitalized children.

Method: This prospective observational study included children hospitalized from March 6 to 20, 2017 in the participating centers. Children aged 0 to 18 years were included, except premature infants. Children hospitalized < 24h or >30 days were excluded. Data was recorded in e-Pinut internet tool (www.epinut.fr), allowing the calculation of indices according to French standards.

Results: Among the 1518 children included, 1178 were analyzed (mean age: 5.7 ± 5.5 years). At admission, a Waterlow index < -2SD was present in 10.5% of cases. The mean LOS was 5.2 ± 5.6 days. The mean weight change during hospitalization was +0.7 ± 3.8%. Weight loss >2.5% was observed in 9.8% of cases. LOS was not different according to nutritional status at admission (6.0 ± 6.2 days vs. 5.0 ± 5.6 days, NS). LOS was longer in the 39% of children with chronic diseases (6.9 ± 6.9 days vs. 4.1 ± 4.4 days, p&LT; 10−3). Children with a Waterlow index &LT; -2SD at admission had a higher weight change than children with a Waterlow index >-2SD (3.1 ± 4.9% vs. 0.4 ± 3.5%, p&LT; 10−3). Children with weight loss >2.5% had a longer LOS (6.9 ± 6.2 days vs 5.0 ± 5.5 days, p &LT; 10−3) and received more nutritional support at discharge (11.0% vs. 3.5%, p=0.03).

Conclusion: LOS was longer in children with weight loss >2.5%. The nutritional status at admission had no influence on LOS. Weight gain in children with a Waterlow index &LT; -2SD and increased nutritional support in children who lost weight suggests appropriate nutritional management, promoted by the awareness of malnutrition.

Disclosure of interest: ADL: Research support from Nutricia, Nutrition Clinique-France

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Metformin responsivity of obesity-related idiopathic intracranial hypertension in 2 hyperinsulinemic children with impaired glucose tolerance. Cases presentation and review of literature

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Objectives and Study: Obesity and its related metabolic imbalances have been associated to idiopathic intracranial hypertension (IIH) in adults and recently in children as well. The interest in IIH [also known as Pseudotumor Cerebri (PTC)] is increasing due to epidemic childhood obesity rates, and in older children it was estimated that 82% of the incidence of PTC was attributable to obesity. There are some evidences of the effectiveness of PTC treatment with metformin, only in women with concurrent polycystic ovary syndrome or hyperinsulinemia. We describe a successful PTC treatment with metformin in two unrelated obese children, with hyperinsulinism and impaired glucose tolerance. We review literature on previous use of metformin for PTC treatment in obese children.

Method: Patients baseline clinical and laboratory features are summarized in Table 1.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Gender</th>
<th>Blood glucose levels mg/dL</th>
<th>BMI (Kg/m2) (centile)</th>
<th>Blood glucose curve mg/dL T0/T30/T60/T90/T120</th>
<th>WC cm (centile)</th>
<th>Blood Insulin curve UI/mL T0/T30/T60/T90/T120</th>
<th>Acanthosis nigricans</th>
<th>Onset symptoms</th>
<th>Head MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1</td>
<td>13; Female</td>
<td>108</td>
<td>34.3 (&gt;95%ile)</td>
<td>75/113/125/103/128</td>
<td>111 (&gt;95%ile)</td>
<td>27/209/249/226/52</td>
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<td>Cephalgia, photophobia, diplopia, vomiting</td>
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<tr>
<td>Pt2</td>
<td>12; Male</td>
<td>100</td>
<td>28.6 (&gt;95%ile)</td>
<td>94/164/167/131/154</td>
<td>110 (&gt;95%ile)</td>
<td>19/104/197/146/32</td>
<td>Neck</td>
<td>Cephalgia, diplopia, shimmering lights/colour ed centres</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood glucose levels mg/dL</td>
<td>HOMA-IR index [(glucose xinsulin)/405]</td>
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<td></td>
<td>LDL Cholesterol mg/dl</td>
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<td></td>
<td></td>
<td>17.6</td>
<td>10.3</td>
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<td>75</td>
<td>53</td>
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<tr>
<td></td>
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<td>WC cm (centile)</td>
<td>Blood glucose curve mg/dL T0/T30/T60/T90/T120</td>
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<td>HDL Cholesterol mg/dl</td>
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<td>110/60 (&lt;90%ile)</td>
<td>115/60 (&lt;90%ile)</td>
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</table>

[Table 1. Patients’ clinical and laboratory features]
Legend to Table 1: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: Blood pressure; GGT: gamma glutamyl transpeptidase; HDL: High-density lipoprotein; HOMA: Homeostasis Model Assessment; LDL: low-density lipoprotein; LPOP lumbar puncture opening pressure; NE: Not Evaluable (black race); MRI: magnetic resonance imaging; IR: insulin resistance; WC: waist circumference.

At beginning patients were treated with mannitol, acetazolamide, lumbar puncture opening pressure and continued for 2 weeks acetazolamide (in one case associated to furosemide). Due to only partial clinical response, metformin was added at the dose of 1 g/day for 1 month, then 1.5 g/day for 1 more month. Lifestyle changes were encouraged.

**Results:** After starting oral hypoglycemic treatment HOMA, glucose tolerance and all PTC signs/symptoms started to progressively improve; papilledema completely recovered within 2 months. No significant side effect has been reported. Literature analysis (Pub-Med; Scopus; Google Scholar) did not show data on the use of metformin as treatment of PCT in pediatric age.

**Conclusion:** Obesity and insulin resistance are associated to PCT in children, and in this context, etiologically targeted therapies should be considered. To our knowledge this is the first time that metformin has been successfully used for PCT treatment in pediatric hyperinsulinemic obese patients.
Lymphocyte profile in severely obese children

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Objectives and Study: Obesity is described as a low-grade inflammatory disease that causes co-morbidities in adults. In obese children, macrophage infiltration of adipose tissue is already described but little is known about the blood lymphocyte profile. The aim of our study was to describe the lymphocyte populations in obese children and to look for a link between lymphocyte populations and phenotypes related to obesity.

Method: 207 children (122G, mean age 13.1 ± 2.5 years, mean body mass index (BMI) Z-score 4.8 ± 0.9 SD, mean age of onset of obesity = 3.5 ± 1.8 years) had a phenotypic characterization (history of obesity, metabolic and inflammatory parameters) and lymphocyte phenotyping (total T lymphocytes (CD3), lymphocyte T populations (CD4 / CD8) and total B cells (CD19)).

Results: 91% of children had at least one lymphocyte abnormality compared to pediatric norms (PGen): CD3 < PGen 9% (n = 18) and> PGen 28% (n = 57); CD19 < PGen 20% (n = 42) and> PGen 28% (n = 59); CD4 < PGen 13% (n = 28) and> PGen 34% (n = 70); CD8 < PGen 47% (n = 97) and> PGen 12% (n = 25).

The comparison of the phenotype according to the 3 groups showed that the BMI Z-score was significantly higher for the groups of CD19, CD3 and CD4> PGen (CD19: 5.1 ± 1.1 DS vs 4.7 ± 1.1 DS p = 0.016, CD3: 5.3 ± 1.1 vs 4.6 ± 1.1 p = 0.0002, CD4: 5.1 ± 1.2 vs 4.7 ± 1.2 p = 0.02). When the cohort was categorized in tertiles, obese children in the 3rd tertile with the most severe obesity (BMI Z-score [5.1 - 8.7] SD) also had higher CD3 and CD19 levels (CD3: 2.03 ± 0.61vs 1.73 ± 0.39, p &LT; 0.001, CD19, 0.56 ± 0.25 vs 0.44 ± 0.15, p &LT; 0.001). The biological inflammatory syndrome was also significantly higher in the CD19> PGen group with higher CRPus (7 ± 5.8mg / L vs 5.21 ± 5.0mg / L, p = 0.02) and fibrinogen (4 , 2 ± 1.2g / L vs 3.7 ± 0.7g / L, p = 0.012). Finally, HOMA-mediated insulin resistance was also higher for the CD3> PGen group (4.06 ± 4.5, vs 3 ± 1.64 p = 0.04) and the CD8 group> PGen (4.96 ± 6.6, vs 2.97 ± 1.9 p = 0.03).

Conclusion: Our results demonstrate that severely obese children have abnormal lymphocyte phenotype suggesting systemic inflammation that is probably related to the early onset adipose tissue infiltration and linked to later comorbidities.
Metabolic and vascular comorbidities in insulin-resistant obese children

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Objectives and Study: Insulin-resistance (IR) is developed at early ages in childhood obesity, being the principal factor in the beginning of metabolic syndrome and cardiovascular disease. The aim of this study was to examine vascular and metabolic comorbidities in obese children with and without IR, measured by HOMA (homeostatic model assessment) index.

Method: A prospective observational study was conducted in 104 children aged 8-18 years old, 87 with obesity and 17 with normal weight. Children with obesity were subsequently sub-categorized as IR and non-IR (nIR) obese children using the 98th percentile for HOMA-IR index in a control group (HOMA-IR≥3.6). Anthropometric assessment was performed, child's weight, height, waist and arm circumference, and tricipital and subcapular skinfolds were collected using a standardised technique and z-scores were assessed; BMI-for-age z-score was calculated (±2 SD according to WHO references). Blood pressure (BP) was recorded using a validated protocol. HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides (TGA), glucose, insulin and uric acid were measured and HOMA-IR calculated. High-resolution ultrasound measurement of arterial stiffness and intima-media thickness was performed. The study plan was approved by the Hospital’s Ethics Committee's.

Results: Established HOMA-IR cut-off point derived in 45 nIR obese children and 42 IR obese children. Obese children did not show anthropometric differences when were compared; statically significant differences were found in all of those variables when compared both groups with the control group. Significant differences were shown between both the control and nIR in HDL-C and insulin, and in HDL-C, TGA, insulin, HOMA-IR and uric acid when compared with IR. IR showed higher significant levels of TGA, glucose, insulin, HOMA and uric acid, and lower of HDL-C than nIR. Systolic blood pressure (SBP) was higher in IR than in nIR and the control; no differences were found in diastolic blood pressure (DBP). No differences were shown between the control group and nIR when assessing arterial stiffness and intima-media thickness (IMT). IR showed higher β-stiffness, elasticity modulus (Ep) and pulse wave velocity (PWVβ) than the control group, and higher Ep and PWVβ than nIR; no differences were found in IMT.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=17)</th>
<th>Non-IR Obese (n=45)</th>
<th>IR Obese (n=42)</th>
<th>p-value Control vs. nIR</th>
<th>p-value Control vs. IR</th>
<th>p-value nIR vs IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI z-score</td>
<td>-0.27±0.73</td>
<td>2.80±0.92</td>
<td>2.73±0.66</td>
<td>0.000</td>
<td>0.000</td>
<td>0.680</td>
</tr>
<tr>
<td>LDL-Cho (mg/dL)</td>
<td>99.12±21.12</td>
<td>103.79±22.42</td>
<td>106.36±31.77</td>
<td>0.463</td>
<td>0.546</td>
<td>0.923</td>
</tr>
<tr>
<td>HDL-Cho (mg/dL)</td>
<td>63.00±12.30</td>
<td>51.52±9.40</td>
<td>45.86±8.69</td>
<td>0.000</td>
<td>0.000</td>
<td>0.005</td>
</tr>
<tr>
<td>TGA (mg/dL)</td>
<td>91.06±81.35</td>
<td>77.29±32.25</td>
<td>124.07±71.72</td>
<td>0.591</td>
<td>0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.66±1.25</td>
<td>4.85±1.22</td>
<td>5.49±1.03</td>
<td>0.600</td>
<td>0.011</td>
<td>0.011</td>
</tr>
<tr>
<td>SBP z-score</td>
<td>-0.04±0.71</td>
<td>0.49±0.75</td>
<td>0.94±1.07</td>
<td>0.016</td>
<td>0.001</td>
<td>0.040</td>
</tr>
<tr>
<td>Beta</td>
<td>2.94±0.42</td>
<td>3.28±0.81</td>
<td>3.47±0.79</td>
<td>0.369</td>
<td>0.005</td>
<td>0.186</td>
</tr>
<tr>
<td>Ep (kPA)</td>
<td>34.82±6.24</td>
<td>38.10±9.09</td>
<td>42.64±8.83</td>
<td>0.186</td>
<td>0.002</td>
<td>0.021</td>
</tr>
</tbody>
</table>
| PWVβ              | 3.56±0.32            | 3.68±0.35           | 3.89±0.41       | 0.257                   | 0.002                  | 0.008            

[Table 1. Comparison between groups]
**Conclusion:** In this study, children with obesity and IR showed higher metabolic and vascular alterations than their counterpart, while both were anthropometrically comparable. Furthermore, the IR group presented differences between the control group that were not shown when comparing the last with nIR. These results reflect that insulin resistance in obese children may be related to early vascular and metabolic comorbidities.

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Objectives and Study: Reaching optimal nutritional intake can be challenging in critically ill infants. Infants are particularly vulnerable to malnutrition because of their limited body reserves and higher nutrient requirements for growth and development. One possible way of decreasing nutritional deficits is the use of protein and energy-enriched (PE) infant formulas. The aim of this study was to assess the effect of PE-formula in infants admitted to the PICU by means of assessing tolerability and nutritional status in this vulnerable group.

Method: Retrospectively, medical records from 470 infants (< 1 year) using PE-formula (Infatrini®, Nutricia N.V., Zoetermeer, The Netherlands) admitted to a multidisciplinary tertiary PICU from January 2007 until June 2017 were analysed. To be eligible, PE-formula was given for at least two weeks and with a minimum of 80% of total caloric requirement. Changes in nutritional status were determined as the difference between weight-for-age (WFA) z-scores at the start and end of PE-formula use. A WFA z-score < -2 was used to indicate acute malnutrition. GI symptoms, including gastric residual volume, constipation and vomiting were evaluated as tolerance parameters.

Results: Seventy infants were included; mean age 76 days, median length PICU-stay 34.9 days and median duration PE-formula use of 29.2 [IQR 20.9 - 54.3] days. Predominant admission diagnoses were; post-cardiac surgery (n=24), respiratory failure (n=13), cardiac failure (n=8) and neurologic disease (n=4). At the start of PE-formula, 33 (47%) infants were acutely malnourished. This was decreased to 23 (33%) when PE-formula was stopped. Of these 23 infants, 19 were already malnourished before starting the PE-formula and 4 were new cases. Infants received 2.01 (± 0.43) times the calculated resting energy expenditure (according Schofield equation1). A mean increase in WFA z-score of 0.48 (± 1.10) and a median weight gain of 6.05 (± 4.82) gram/kg/day was observed. Fifty (72%) infants had an increase in WFA z-score, whereas 65 (93%) had an absolute gain in body weight. A lower WFA z-score at start (P=0.001) and a lower WFA z-score at birth (P=0.006) were positively associated with increase in WFA z-score. The median 24 hour gastric residual volume of the infants was 9.1 ml [IQR 3.4 - 16.0] per kg body weight. Three (4%) infants were treated for diarrhea and three infants for vomiting while using the PE-formula.

Conclusion: Protein and energy-enriched formula seems to be well tolerated in critically ill infants. During the use of PE-formula the majority of infants gained weight and had an increase in WFA z-score.


Disclosure of interest: R. Eveleens received a research grand from Nutricia Research.

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The effect of inflammation on body composition in children admitted to a tertiary hospital

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Objectives and Study: Malnutrition is prevalent in children and adults with chronic illness and high rates are observed in the inpatient paediatric population. The development of disease related malnutrition is multi-factorial. The presence of chronic inflammation has been associated with altered body composition (BC) in certain inflammatory diseases. We tested the hypothesis that chronic inflammation in children, resulting from any pathological process, is associated with malnutrition, lower lean mass (LM) and higher fat mass (FM), compared to children with other diseases requiring specialist inpatient paediatric care.

Method: A prospective study at a tertiary paediatric hospital recruited 154 patients, at admission, aged 4.6-17.6 years (mean 10.8), 50% female. Baseline data was collected on diagnoses, steroid prescription, nutritional support and activity level. CRP and platelet counts were recorded where blood tests had been performed. Anthropometric and BC measurements were performed using a range of techniques including Dual-energy X-ray Absorptiometry (DXA).

44 of these subjects were identified as having primary inflammatory disease and/or systemic inflammation (CRP ≥50 mg/ml and/or platelets ≥450 x 10⁹/L) and were analysed compared to (1) healthy reference children and (2) subjects within the cohort without inflammation.

Results: Subjects with inflammation had lower height (mean -0.72 SDS, p=0.007), lower LM (mean -1.04 SDS, p=0.002), lower Lean Mass Index (LMI=LM (kg)/height²) (mean -0.62 SDS, p=0.036) and higher Fat Mass Index (FMI) (mean 0.54, p=0.035) compared to healthy reference children. There was, however, no significant difference when compared with patients without inflammation. Linear regression modelling of the whole cohort, of 154 subjects, was performed using: presence of inflammation; high-dose steroid use; mode of feeding and activity level (with four categories ranging from ‘ambulatory taking part in sports’ to ‘wheelchair user not involved in sport’) as potential predictors. This modelling suggested useful predictors for low LMI were artificial nutrition and low activity levels (orally fed β -1.03, p=0.023, enterally fed β -0.62, p=0.048, parental nutrition β -0.9, p=0.015; wheelchair user not involved in sport β -3.36, p=0.002). For FMI high-dose steroids were found to be a useful predictor (β 0.81, p=0.023). Presence of inflammation was not a useful predictor for LMI or FMI.

Conclusion: Malnutrition was common in children with inflammation, when compared to healthy reference children, although no significant difference was identified between inpatients with and without inflammation. It is possible that the indicators used were insufficiently informative to demonstrate that inflammation had a significant adverse effect on anthropometric and BC measurements, when compared to non-inflammatory chronic diseases affecting an inpatient paediatric population. The observation of increased FMI in the context of high-dose steroids may suggest a relationship with chronic inflammation but needs further investigation.

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Bioelectric impedance vector analysis (BIVA) and clinical outcome in hospitalised children

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Objectives and Study: Bioelectric impedance analysis (BIA) is a widely used, simple bedside technique, but clinical use is limited by the convention that raw measurements are converted to body composition, using equations that are potentially inappropriate. The use of the raw bioelectric impedance vectors (BIV), resistance (R), reactance (Xc) and phase angle (PA) - suggested to indicate body fluid, cell mass and cell health respectively - may be an alternative for monitoring disease progression and/or treatment. However, clinical experience of BIV in children is limited and previous studies have not standardised for age. We investigated predictors of BIV and their ability to predict clinical outcomes in children with complex diagnoses admitted to a tertiary children's hospital.

Method: R, Xc and PA were measured using BODYSTAT Quadscan 4000 on admission in 70 children aged 4.6-16.8 years (mean 10.0). R and Xc were indexed by height (H) and BIVSDS generated for age and sex using data from healthy children. Potential predictors (activity, wheelchair use, steroid treatment, use of enteral/parenteral nutrition, malnutrition risk by PYMS, STAMP and StrongKids tools); and clinical outcomes (greater-than-expected length-of-stay (LOS), complications (unplanned transfer to ICU, increased artificial nutrition, infection requiring antibiotics)) were recorded at discharge.

Results: Mean R/HSDS was significantly higher (0.99 (SD 1.32)) and PASDS significantly lower (-1.22 (1.51)) than the population mean, but with a wide range for all BIVSDS. R/HSDS was significantly different in children classified as low, medium or high risk by STAMP (0.13 (1.04), 0.97 (1.25), 1.49 (1.37), p=0.02) and StrongKids (-0.06 (1.04), 0.95 (1.08), 1.84 (1.56), p=0.001) but not PYMS. No other significant predictors of BIVSDS were identified. BIVSDS were not significantly different in patients with or without adverse outcomes, although R/HSDS was higher in children with increased LOS (mean difference 0.42 (95% CI = -0.26 to -1.11) or complications (mean difference 0.49 (95% CI -0.34 to 1.33).

Conclusion: This group of complex patients had abnormal mean BIVSDS suggestive of reduced hydration and poor cell health according to conventional interpretation of BIV. R/HSDS was significantly higher in patients predicted to be at higher risk by STAMP or StrongKids malnutrition screening tools. However, other factors considered as clinical predictors showed no significant association, and BIVSDS were not significantly related to clinical outcomes; possibly reflecting the necessary use of generic predictors and outcomes in this heterogeneous population. Children with adverse outcomes showed a trend towards higher R/HSDS, suggesting lower hydration. Further investigation in specific patient groups, including those with acute fluid shifts and using disease-specific outcomes, may help to better define the clinical role of BIV.

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A review of copper deficiency in paediatric patients on long-term jejunal nutrition

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Objectives and Study: Copper is a trace element essential for a number of vital processes within the body. It is mainly absorbed in the duodenum. Copper deficiency is a rare but potentially serious condition, manifesting as haematological derangement, sensory impairment and neuropathies. It is most commonly seen in patients who have had bariatric surgery. Patients who are jejunally-fed long-term will logically be at risk of copper deficiency due to where their nutrition enters the GI Tract, as feed is delivered beyond the site of copper absorption.

Aims:
1. To review the detection and management of copper deficiency in jejunally fed patients managed at a single tertiary care centre.
2. To investigate feeding tube position as a potential contributor to copper malabsorption.
3. To close the loop on a previous audit performed in our department, which found that 40% of jejunally fed patients were copper deficient.

Methods: Case notes of all patients on long-term jejunal nutrition were reviewed. Type of Jejunal feeding was noted. Results from trace element screens were recorded and imaging was checked by specialist radiologists to assess tube position. These results were then correlated with serum copper levels, to look for any links to low copper and an inadequately positioned tube.

Results: 22 patients were included in this study, (14 Males, 8 Females, mean age 8 years (range 1-21 years)). 7 of these patients had a Roux-en-Y Jejunostomy, 12 had a PEGJ, 2 had a GJ Button, and 1 had an NJ tube. Nearly half of the patients were suffering from Cerebral Palsy. 2 patients had never had copper levels checked. There was no relationship between type of feed, its copper content, and serum copper levels. 3 of these patients (13.6%) had been diagnosed with a low serum copper level, down from 40% in our previous audit. 1 patient had a low serum copper and was receiving copper sulphate solution as treatment. 1 patient had previously low copper levels with normalisation on recent testing, but remained on treatment. The third patient was on a lower than standard maintenance dose for previous low copper that had subsequently normalised. As an additional point, 4 patients also had low zinc picked up on their micronutrient screen, one of whom was documented as being prescribed supplements. Tube position was generally found to be good; we did notice that a poorly positioned tube of any type, or a tube requiring regular adjustment/change resulted in poorer micronutrient absorption. Assessment of neurological complications from copper deficiency was difficult given the co-morbidities of this patient cohort. No obvious haematological derangement was observed.

Conclusion: The number of enterally-fed patients is increasing in the UK, both in the adult and paediatric populations. Micronutrient management is becoming an increasingly recognised part of care. Copper deficiency is under-recognised in children on jejunal nutrition. When detected, treatment was established and successful. Work must be done in implementing guidance on the screening of micronutrient deficiencies as a whole, however there are obvious practicality issues with achieving this in such a population.

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Development of a screening tool for undernutrition in children and adolescents with cerebral palsy

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²Griffith University, Gold Coast, Australia
³Children's Hospital of Wisconsin, Milwaukee, United States

Objectives and Study: To develop a screening tool for use in children with cerebral palsy (CP) to identify those, in a community setting, who were undernourished and would benefit from nutrition interventions.

Cross-sectional, observational study. Ethical approvals have been obtained.

Methods: Data for 72 children with CP aged between 2 and 18yrs have been collected and analysed. The average ± SD age of participants was 7.5 ± 4.1yrs with the majority being male (67%). Gross Motor Function Classification System Levels were: I=20, II=24, III=5, IV=11, V=12 Predominant motor impairments were spasticity (n=49), dyskinesia (n=15) and hypotonia (n=8). Children with feeding tubes were excluded, 32% of children had seen a dietician or speech pathologist in the previous 12 months for feeding or nutrition concerns. Data collection for this study is ongoing.

Full dietetic assessment was completed by experienced paediatric dieticians utilising the Pediatric Subjective Global Nutrition Assessment (SGNA). Children were classified as A = well-nourished, B = moderately undernourished, or C = severely undernourished. Height/length was measured or estimated from knee height using published equations. Body weight, triceps (TSF) and subscapular skinfold thicknesses (SSSF) and mid upper arm circumference (MUAC) were measured. Body mass index (BMI) was calculated as weight (kg)/ height (m)². Anthropometric data were converted to Z-scores to account for age and gender differences. Cut-offs to determine undernutrition (≤ -2 Z-scores) were applied.

Parents/caregivers answered a series of 31 questions based on Arvedson's “Red Flags” (EJCN 2013, 67:S9-S12) related to their child’s feeding ability and nutritional status. Sensitivities (sn) and specificities (sp) to identify moderately or severely undernourished children (SGNA B or C; weight for age, and BMI for age Z-scores of ≤ -2) were calculated for each question.

Results: Using the SGNA, 47 children (65%) were considered well-nourished, 19 (26%) moderately undernourished and 6 (8%) severely undernourished. The number of children with Z-scores of ≤ -2 for each of the anthropometric outcomes were: Height = 16 (22%), weight = 22 (31%), BMI = 17 (24%), MUAC = 10 (14%), TSF = 2 (3%), SSSF = 0. The screening questions with the highest sensitivity (sn (95% CI) and specificity (sp (95% CI) for identifying undernourished children by SGNA are included in table 1. A single screening question of “Do you think your child is underweight?” was able to accurately identify 74% of undernourished children and accurately exclude 71% of well-nourished children.
<table>
<thead>
<tr>
<th>Question</th>
<th>SGNA Sensitivity (95% CI)</th>
<th>SGNA Specificity (95% CI)</th>
<th>Weight Z-score Sensitivity (95% CI)</th>
<th>Weight Z-score Specificity (95% CI)</th>
<th>BMI Z-score Sensitivity (95% CI)</th>
<th>BMI Z-score Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you think your child is obviously underweight?</td>
<td>0.54 (0.33 - 0.72)</td>
<td>0.90 (0.77 - 0.96)</td>
<td>0.58 (0.36 - 0.77)</td>
<td>0.87 (0.74 - 0.94)</td>
<td>0.53 (0.30 - 0.75)</td>
<td>0.82 (0.69 - 0.90)</td>
</tr>
<tr>
<td>Do you think your child is underweight?</td>
<td>0.74 (0.54 - 0.87)</td>
<td>0.71 (0.56 - 0.82)</td>
<td>0.75 (0.53 - 0.89)</td>
<td>0.68 (0.53 - 0.80)</td>
<td>0.60 (0.36 - 0.80)</td>
<td>0.59 (0.45 - 0.72)</td>
</tr>
<tr>
<td>Does your child have problems gaining weight?</td>
<td>1.00 (0.83 - 1.00)</td>
<td>0.62 (0.46 - 0.75)</td>
<td>1.00 (0.83 - 1.00)</td>
<td>0.62 (0.46 - 0.75)</td>
<td>0.87 (0.62 - 0.96)</td>
<td>0.51 (0.37 - 0.65)</td>
</tr>
<tr>
<td>Does your child find most mealtimes tiring?</td>
<td>0.52 (0.34 - 0.71)</td>
<td>0.60 (0.44 - 0.73)</td>
<td>0.38 (0.21 - 0.59)</td>
<td>0.53 (0.38 - 0.66)</td>
<td>0.47 (0.23 - 0.70)</td>
<td>0.56 (0.42 - 0.69)</td>
</tr>
<tr>
<td>Would you describe most mealtimes as stressful?</td>
<td>0.48 (0.30 - 0.67)</td>
<td>0.61 (0.47 - 0.74)</td>
<td>0.50 (0.31 - 0.69)</td>
<td>0.62 (0.47 - 0.74)</td>
<td>0.37 (0.18 - 0.61)</td>
<td>0.57 (0.43 - 0.69)</td>
</tr>
<tr>
<td>Does your child experience retching/ vomiting at meal times or after eating/drinking?</td>
<td>0.48 (0.30 - 0.67)</td>
<td>0.53 (0.39 - 0.67)</td>
<td>0.50 (0.37 - 0.63)</td>
<td>0.41 (0.23 - 0.61)</td>
<td>0.59 (0.36 - 0.78)</td>
<td>0.56 (0.43 - 0.69)</td>
</tr>
<tr>
<td>Does your child have any problems eating compared to other children of his/her age?</td>
<td>0.62 (0.41 - 0.79)</td>
<td>0.60 (0.45 - 0.72)</td>
<td>0.76 (0.53 - 0.90)</td>
<td>0.64 (0.50 - 0.76)</td>
<td>0.76 (0.53 - 0.90)</td>
<td>0.58 (0.45 - 0.70)</td>
</tr>
<tr>
<td>Does your child have any problems drinking compared to other children of his/her age?</td>
<td>0.64 (0.45 - 0.80)</td>
<td>0.53 (0.39 - 0.67)</td>
<td>0.68 (0.47 - 0.84)</td>
<td>0.54 (0.40 - 0.67)</td>
<td>0.59 (0.36 - 0.78)</td>
<td>0.49 (0.36 - 0.62)</td>
</tr>
</tbody>
</table>

**Conclusion:** Parent reported screening questions are a simple, feasible, low-cost method that have the potential to identify children with CP in a community setting who are at risk of undernutrition. Following completion of data collection, further statistical analysis will determine which combination of questions has the highest sensitivity and specificity for identifying children with undernutrition in this population. Further validation of the 31 potential screening questions for identifying children with feeding difficulties has been conducted and will be submitted in a separate abstract.

**Disclosure of interest:** This research has been funded by Danone, Nutricia Research

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NUTRITION - Clinical nutrition

N-P-045

TASTE Treatment And Support for Turicky Eaters: Preliminary results from an innovative feeding rehabilitation programme

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Objectives and Study: Behavioural feeding difficulties affect a substantial proportion of children, some of whom remain dependent on gastrostomy feeds or require oral nutritional supplements, despite their underlying medical condition having been resolved. Similarly, there are children on a highly restricted diet, due to sensory processing disorders, autism or previous swallowing difficulties. Despite the major healthcare burden caused by these patients as well as substantial impact on their families, limited programmes providing holistic support are currently available in our region. Our aim was to develop a structured programme providing intensive support for children with gastrostomy feeding, oral supplement dependencies or very restricted diet, in order to improve or fully normalise eating pattern.

Method: TASTE (Treatment and Support for Tricky Eaters) is an intense feeding rehabilitation programme running for 2 hours/day for 5 consecutive days. A multi-disciplinary team (paediatric gastroenterologist, dietitian, speech and language therapist, psychologist, play therapist) provides food based play activities, coaching and support to max 4 children (age matched) and their parents/carer.

Over 2 years (2014-2016) 7 sessions took place, involving 25 children (1 was lost to follow-up). Patients had a telephone assessment 2 weeks later, to monitor progress and a clinic review at 3 and 6 months to monitor growth and intake.

Inclusion criteria: Patients are recruited on the basis of their behavioural feeding problem, regardless of the heterogenic underlying medical condition (genetic disorders, prematurity, severe gastro-oesophageal reflux disease, autism spectrum disorder, post tracheo-oesophageal fistula, etc.). All children recruited had behavioural feeding difficulties making them still dependent on gastrostomies (54% - 13/24 children), oral supplements (21% - 5/24 children) or having a very restricted diet (25% - 6/24 children).

Outcome measures: Personalised goals were set for each child ranging from stopping or reducing supplemental feeds to behavioural improvements.

Results: 75% (18/24) of patients achieved their set goals; 46% of them within 6 months from TASTE intervention. 6/13 children recruited on gastrostomy feeds were able to get their gastrostomy removed, having stopped using it for a minimum of 3 months. The remaining 7 were not considered able to suspend gastrostomy feeding, but in 3 of them goal was achieved by reducing the amount of enteral nutrition.

In the oral supplements group (5 patients): 60% (3/5) had their supplements stopped and 1 child managed to reduce supplements by 50%. Only 1/6 patients in the restricted diet group failed to reach the individually set target.

Conclusion: Despite the relatively small and diverse cohort, TASTE has shown promising results in helping children to overcome behavioural feeding disorders. This is a wide spectrum definition but there is no reason TASTE could not be applied to a vast number of patients. At the heart of our results is the family therapy that we offer to patients. By enabling parents to be confident in changing behaviour around meal-times, children do make progress. Crucial to the success of the intervention is recruiting families who are ready to make the changes in their attitude to meal-times.

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Medical and surgical therapies for the treatment of gastrointestinal dystonia in children with severe neurodisability - A systematic review

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Objectives and Study: In children with severe neurodisabling conditions the clinical constellation of pain behaviour, retching, bloating, abdominal distension and constipation can be referred to as gastrointestinal dystonia (GID). These problems tend to present in enterally fed patients who may have already had antireflux surgery. Suggested therapies have included extensive pharmacopenia and jejunal feeding, but the evidence base for such therapies remain obscure.

To inform a joint BSPGHAN/RCPCH guideline development for GID, we aimed to appraise the published evidence on the medical and surgical treatments for GID via systematic review of the literature and to suggest where deficit in the literature could be addressed with guidance.

Method: Systematic retrieval of data for patients < 18yrs with severe neurodisability and gastrointestinal symptoms. Outcomes sought; weight gain, longitudinal growth, pain, quality of life and mortality. We excluded papers where outcomes were the treatment of gastro-oesophageal reflux alone. Electronic searches of Cochrane library, Pubmed (to Nov 2017) and Medline (1946-Nov 2017) were made using the following keyword and MeSH terms; cerebral palsy, neurodisability, child, nutrition, foregut dysmotility, neurogastroenterology, prokinetic, domperidone, baclofen, aprepitant, fosprepitant, levopramazine, nabilon, jejunostomy and retching. Hand searches of meetings of relevance and personal collections were also performed. Two authors independently assessed the level of evidence (EL) was assessed using SIGN (Scottish Intercollegiate Guidelines Network) methodology (http://www.sign.ac.uk) a third author arbitrated.

Results: Search strategy yielded 2811405 hits. Combination searches reduced this to 6064 titles and abstracts. 32 medical and 27 surgical studies were identified as potential studies and reviewed in full, including 1 guideline and 3 Cochrane reviews. 30/32 medical and 18/27 surgical studies were excluded as they were not relevant to our focused clinical question or where specific patient group could not be separated from general data. 2 medical studies related to parenteral nutrition (PN) were included and 9 surgical studies relate to jejunal feeding were included.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>No of studies (no of patients)</th>
<th>EL</th>
<th>Outcomes and comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN</td>
<td>2 (13)</td>
<td>3</td>
<td>Weight gain, cessation of pain, improved feed tolerance post Rx.</td>
</tr>
<tr>
<td>Gastro Jejunal (transpyloric) tube</td>
<td>4 (401)</td>
<td>3</td>
<td>Some weight improvement, frequent tube replacements, 1 study 15% mortality</td>
</tr>
<tr>
<td>Witzell jejunal tube</td>
<td>1 (33)</td>
<td>3</td>
<td>Some growth improvement, volvulus, no mortality data.</td>
</tr>
<tr>
<td>Primary jejunal button</td>
<td>1 (16)</td>
<td>3</td>
<td>Improvements in weight, volvulus, 0 mortality</td>
</tr>
<tr>
<td>Roux and Omega jejunostomies</td>
<td>3 (27)</td>
<td>3</td>
<td>Long term tolerance and growth report, 1 mortality reported.</td>
</tr>
</tbody>
</table>

[Table 1]

Medical data are limited to PN for treatment of GID. Surgical data, although low EL, supports jejunal feeding for growth and symptoms, permanent jejunal feeding is reported with Roux, omega ostomies and primary jejunal buttons.

**Conclusion:** The data for treatment of GID are limited and make developing evidence based guidelines inappropriate. Invested health professional should focus on sharing of experience of specialist multidisciplinary teams, increasing experience and data on novel pharmacopenia. The authors are now developing consensus based guidelines via Delphi process that will aid the standardisation of care, audit of practice and development of research of medical therapies.

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Immunoregulatory effect of Parmigiano Reggiano cheese in children with cow’s milk allergy

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Objectives and Study: Preliminary evidence suggest that fermented food Parmigiano Reggiano cheese (PR), through the activity of peptides produced during the fermentation process, could modulate immune response in children with cow’s milk allergy (CMA). We aimed to evaluate the PR tolerance rate, the potential effect on oral tolerance acquisition, and the immunoregulatory actions exerted by PR-derived peptides in peripheral blood T CD4+ lymphocytes of CMA children.

Method: Challenge confirmed IgE-mediated CMA children consecutively observed at a tertiary center for pediatric allergy were considered eligible for the study. Oral food challenge (OFC) for PR (up to the maximum dose of 13 gr of PR aged 36 months) was performed in all subjects. According to the OFC’s result, patients were allocated to one of the two groups of 12 m dietary intervention: Group 1, children tolerant to PR who continued a cow milk proteins (CMP)- free diet, but consumed 13 gr of PR daily; group 2, children intolerant to PR, who continue CMP-free diet only. After 12m a OFC was performed to investigate the possible acquisition of oral tolerance to CMP. We also evaluated, the immunoregulatory actions exerted by PR-derived peptides (obtained by High Performance Liquid Chromatography, HPLC) in peripheral blood T CD4+ lymphocytes from CMA affected children. Cells were incubated for 48 h, and IL-13 and IL-10 production was assessed in cell supernatant by ELISA.

Results: 67 IgE-mediated CMA patients (age range 1-10 yrs) were enrolled. At baseline, 29 children (43.3%) tolerated PR and were assigned to Group 1. At the end of the study period (12 m), the rate of oral tolerance acquisition for CMP was higher in Group 1 (41.4% vs 5.3%, p<0.05). The stimulation of peripheral blood T CD4+ lymphocytes from Group 1 with PR-derived peptides resulted in a significant increased production of IL-10, but not of IL-13.

Conclusion: PR is tolerated by a high rate of CMA children, in these patients the regular consumption of PR facilitates oral tolerance acquisition through, at least in part, a modulation of IL-10 production by CD4+T cells.

Disclosure of interest: The study was supported at least in part by an unrestricted grant from Parmigiano Reggiano Cheese Consortium, Reggio nell’Emilia (RE), Italy, devoted to Department of Translational Medical Science, University of Naples “Federico II” Naples, Italy.

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**Prevalance of malnutrition in hospitalized children**

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**Introduction:** This study aims to investigate the distribution of malnutrition and disease, detection of malnutrition prevalence, effects of hospitalization on nutritional status.

**Methods:** Four hundred children at the age of 1 month to 18 years who were hospitalized and followed at the inpatient pediatric clinics of Sisli Hamidiye Etfal Training and Research Hospital in the period between August 2014 and May 2015, were included in the study. Within the first 48 hours after hospitalization and discharged at the last 24 hours, body weight, height was measured. The prevalence of malnutrition during hospital admission and discharge of patients was determined.

**Results:** Malnutrition was observed at 56.2%, 38.4%, 30%, 28.9% rates, in children having malignancy, neurological diseases, infection diseases, gastroenterological system diseases, respectively. 31.5% of all the subjects had acute malnutrition at discharge. It is found an increased prevalence of malnutrition 2-6 years of age and 10-18 years of age at discharge. The prevalence of malnutrition decreased in the 1 month-2 age group and 6-10 age group between admission and discharge. Among the groups with high number of patients when evaluated according to hospitalization criteria, the highest malnutrition rate was found in malignity (56.2%), neurology (38.4%) and infection (30%) groups. The lowest rate of malnutrition was found in allergy (0.002%), endocrine (0.002%), heart diseases (0.002%) and metabolic diseases (0.002%) groups. Diseases with more patients in the group when assessed according to system only the prevalence of malnutrition were decreased in the infection group at discharge.

**Conclusion:** Hospitalization of children affects the nutritional status adversely in general, and increases the high frequency of malnutrition. That's why calori calculation according to childrens' age, diagnosis and needs should be evaluated and it's important to prevent them from starving.

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Teduglutide (GLP-2) as treatment in children with short bowel syndrome/intestinal failure and parenteral nutrition

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Objectives and Study: Intestinal failure (IF) due to Short Bowel Syndrome (SBS) requires the use of long-term parenteral nutrition (PN) in children. Long-term PN is associated with the development of liver disease, catheter infections and increased morbidity and mortality. A major goal of treatment of IF is therefore to improve intestinal adaptation in order to reduce the need for PN. Teduglutide (GLP-2, glucagon-like peptide-2) is a new drug for the treatment of IF in adults, but pediatric data is limited. In 2017 Norway accepted teduglutide for the treatment of children with SBS. Patients aged 1 year and above who were clinically stable following a period of intestinal adaptation after surgery were eligible for treatment. We hereby present the results so far.

Method: Data were collected using hospital records. We compared data on growth, output, ratio of PN vs EN, need for replacement hydration and citrulline levels at baseline and after 6 months of treatment. Measurements of stool/stoma output were based on parents’ estimations and measurements. Calculations of increase or decrease in PN were done by dieticians and based on ratio of energy in enteral vs parenteral nutrition before and after treatment.

Results: 9 children are currently under treatment with teduglutide in Norway, aged between 1 and 10 years. The preliminary results show that tolerance for EN/need for PN, stoma/stool output and need for replacement hydration generally improved in all patients. Tolerance was generally excellent, with only one patient complaining of mild nausea. More specific data including gender, underlying etiology and growth will follow when all data are collected.

Conclusion: Teduglutide can be used in the treatment of children with SBS-IF and may reduce the need for PN and replacement hydration. The experience so far is promising but data is still very limited.

Disclosure of interest: Dag Tveitnes, Svend Andersen and Anne Charlotte Brun have attended an expert meeting hosted by Shire Pharmaceuticals, makers of Revestive (teduglutide).

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Body composition changes of children with congenital heart disease during the perioperative period

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Objectives and Study: Children with congenital heart disease (CHD) are at high risk for malnutrition, and the body composition changes obtained through bioelectrical impedance analysis (BIA) could be a sensitive index for the nutritional evaluation of CHD children during the perioperative period.

Method: Seventy-five children with CHD were enrolled in the study. Their body composition and phase angle (PA) were measured via BIA one day before and one and seven days after open heart surgery. Seventy-five controls were also recruited.

Results: The PA one day after surgery was significantly lower than that one day before surgery and returned to the preoperative level seven days after surgery. However, a repeated-measures analysis of variance (ANOVA) showed that the changes in the body weight, fat mass, free-fat mass, and body cell mass over time were not significant, whereas the changes in the PA over time were significant. The repeated-measures ANOVA indicated that changes in the total body water, edema index, and intracellular water over time were not significant, but the changes in the extracellular water were significantly correlated with time.

Conclusion: The PA might be a sensitive index for the nutritional evaluation of CHD children during the perioperative period. The conditional implementation of BIA has been proposed for the accurate evaluation of the nutritional status of CHD children, which would allow individualized nutritional support and thus improvement of the nutritional conditions and clinical outcomes of CHD children.

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Vitamin D levels in a population of Mexican children in a third level hospital

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Objectives and Study: Vitamin D is important for normal growth and development in children, it also plays a critical role in immune system and bone health. Its deficiency is associated with both infectious and non-communicable diseases as chronic degenerative and others. The prevalence of vitamin D deficiency has increased recently and continues to be underdiagnosed and undertreated. There is limited data about worldwide vitamin D deficiency in paediatric population. In our country, the last survey was done in 2006, and the prevalence of vitamin D deficiency was estimated around 39% (deficiency 16% and insufficiency 23%) in children aged 2-12 years. In our country there is no study about prevalence of vitamin D deficiency in different diseases in paediatric population. The aim of these study was to describe the levels of vitamin D, in children with different diseases who were seen in a third level hospital at Mexico City.

Method: A retrospective study was done. We reviewed 949 clinical charts of children who were screening for serum levels of vitamin D during a period of 3 years (2014 - 2017) at Instituto Nacional de Pediatría in Mexico City.
We evaluated the following variables, gender, age, weight, height, serum levels of 25-hydroxyvitamin D [25(OH)D], Mexican province of origin, and main clinical diagnosis of disease. We defined as group 1 severe deficiency as 25(OH)D serum concentration < 8 ng/ml, group 2 moderate deficiency < 20 ng/ml, group 3 insufficiency < 30 ng/ml, and group 4 sufficient 30 ng/ml or greater. The data is presented in median (minimum-maximum). Statistical analysis was done with Krushall-Wallis. A p-value of < 0.05 was statistically significant.

Results: Of all children, 516 (54.4%) were female and 433 (45.6%) male. Median age was 10.5 years (1-225). There was statistical significance according to vitamin D levels with age (p 0.001) and height (p 0.047). (Figure 1a) Median serum 25(OH)D concentration was 20.3 ng/ml (4.2-74). Group 1 were 38 children (4%), group 2, 424 (44.7%), group 3, 475 (50%), and group 4, 12 (1.3%). (Figure 1b) Most population were from Mexico City 529 children (55.7%), followed by 223 (23.5%) children from Estado de Mexico, and the others from different states of Mexico. (Figure 1c).
According to diseases the main diagnosis found with vitamin D deficiency was obesity, Turner syndrome, type 1 Diabetes Mellitus, Leukaemia, chronic renal failure, allergic diseases (allergic rhinitis and cow’s milk allergy protein). (Figure 1d)
Conclusion: Vitamin D deficiency was quite common in our study. The main diagnosis found with vitamin D deficiency was obesity, considering that Mexico is a developing country with one of the highest youth obesity rates worldwide, we should be aware of it. Endocrinology, gastrointestinal, nephrology and allergic diseases were more associated with vitamin D deficiency. The major population of children were from Mexico City, but it is understandably because our hospital is located in this area.

We should enhance screening of vitamin D deficiency in risk children, in order to prevent associated diseases, with a correct supplementation and lifestyle changes.
NUTRITION - Clinical nutrition

N-P-052

Vitamin D application of a mathematical model to estimate the supplementation doses in a paediatric and adolescent obese population with vitamin D insufficiency/deficiency

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Objectives and Study: Vitamin D (VD) insufficiency is a widespread epidemic linked to different non-musculoskeletal health outcomes such as immune disorders, cancer and metabolic syndrome. Supplementation guidelines and official consensus has not been made with exact therapy dosage and diagnosis criteria. Risk factors linked to VD insufficiency are race, obesity, sunscreen and age (the elderly and children). In obesity, deficiency mechanisms proposed are adipose tissue sequestration and volumetric dilution. Volumetric dilution includes total body weight as a primary variable in the development of this disorder and not just body fat, thus defining total body weight as a factor when deciding supplementation therapy. A single blind longitudinal study regarding volumetric dilution proposed a regression based equation to estimate VD doses in order to achieve sufficiency levels in obese adults. The aim of this study was to apply the same mathematical equation to estimate the VD supplementation therapy in a paediatric and adolescent obese population with VD insufficiency/deficiency.

Method: Longitudinal randomized control study of 2 different doses of oral vitamin D3, 800 IU (control group) or mathematical model calculation (intervention group), prescribed daily for 8 weeks during spring-summer of 2017. The subjects were 15 children aged 6 to 18 years with BMI z-score >1.0 recruited among the Obesity and Adolescence Clinic in the National Institute of Paediatrics, Mexico City. All participants and their families signed an informed consent form. Subjects were excluded if they had any chronic condition or if they were taking medications affecting VD metabolism. 25-hydroxycholecalciferol (25(OH) D) was measured at baseline and 8 weeks after supplementation. Vitamin D deficiency was defined as serum 25(OH)D ≤20 ng/ml and insufficiency as 21-29 ng/ml respectively.

Results: From total sample insufficiency was found in 7/15 (46.6%) subjects and deficiency occurred in 8/15 (53.3%). 7 subjects were assigned to control group and 8 subjects to the intervention group. Mean 25(OH)D was 22.81 ng/ml and 18.55 ng/ml for the control and intervention group respectively. Insufficiency occurred in 4/7 and 3/8 subjects and deficiency was found in 3/7 and 5/8 in the control and intervention group respectively. After intervention, the control group raised an average of 2 ng/ml serum 25 OH D and intervention group raised 6 ng/ ml; however, Fisher’s exact test was performed and no significant difference was found between both groups. There was no statistical significant difference regarding BMI, body fat percent or waist to height ratio. Deficiency remained only in 1/15 (6.6%) subject from total sample.

Conclusion: The application of a mathematical estimation model showed better supplementation outcomes compared to standard dose (800 UI) group, however; no significant difference was found. Different factors influence these results such as environmental factors (season, compliance and sunlight exposure) and a longer follow-up with a bigger population may show different results. Studies with VD supplementation in obese children should continue in order to include its therapy as complementary treatment for this high-risk population.

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**Objective:** To identify the results of allergic testing for diagnosis cow's milk protein allergy in children with history suspected of cow's milk protein allergy.

**Method:** This study is descriptive cross-sectional retrospective cohort study which included children aged less than 5 years who presented with suspected history and clinical symptoms of CMPA at Thammasat University Hospital (both out and in patient) between 2012-2017. Demographic and cow's milk oral challenge data (both at hospital under medical care and at home accidentally challenge) and results of investigation related to CMPA were recorded. Data were analyzed with STATA.

**Results:** Sixty-one patients were enrolled; mean age of onset was 5.02 ± 10.98 months. Most common initial system involvement was gastrointestinal system (60.6%) and cutaneous system (27.9%). Seven patients (11%) presented with more one organ system involvement. There was no difference of clinical presentations between male and female. 48 patients (78.7%) were term infant; average birthweight was 2,978.5 grams. No difference in family history of allergic diseases and smoking. All children had normal growth. Skin prick test to cow's milk protein was identified to be positive in 1 patient (4.4%); positive specific IgE to cow's milk was identified in 2 patients (4.8%). Positive oral challenge to cow's milk protein was identified in 9 patients (14.8%).

**Conclusions:** Clinical presentations without further investigations such as skin prick test, specific IgE or oral food challenge could lead to over-diagnosis of CMPA as only 14.7% of patients were positive to oral food challenge. Oral food challenge is very useful to confirm the diagnosis of CMPA and therefore the appropriate management.

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Reverse Body Mass Index: a good tool to estimate fat mass in overweight and obese children and adolescents at different ages

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Objectives and Study: Considering that the Body Mass Index (BMI) does not have a normal distribution in the pediatric population and that its usefulness for estimating fat mass have been questioned, the rBMI (cm²/Kg) was proposed and it was concluded, in studies carried out in adults, that it was useful and more accurate for this estimate. Our principal aim was to carry out a study in children using as reference the fat mass obtained by DXA and check that the rBMI does have a normal distribution in the studied population and that although both, the rBMI and the BMI are good predictors of the fat mass the rBMI predicts somewhat better the variance of it.

Method: 133 overweight and children and adolescents were included in the study. All of them were attended in the Nutrition and Metabolism Unit at the San Joan University Hospital (Alicante, Spain). They were between 5-15 years of age (mean 11,1 SD 2,6 years). Of them, 57 were female (42,9%). Patients were distributed in two groups of age: Group 1 girls up to 8 and boys up to 9 year of age (n=25). Group 2: from this age to 15 years of age. Height, and weight, were measured in all the patients in order to calculate BMI and rBMI and all of them had a study of fat mass percentage by DEXA. The calculation of rBMI is: \( rBMI = \frac{\text{height (m)}}{\text{weight (kg)}} \)

Results: In the total sample it was proved a good relationship between % Total Fat Mass, % Total fat mass, fat FMI and non fat max index measured by DEXA and BMI in the total sample. (TABLE)

<table>
<thead>
<tr>
<th>iIMC vs</th>
<th>r²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat weight</td>
<td>0.782</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>% Total fat Mass</td>
<td>0.411</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Fat Mass Index</td>
<td>0.819</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Non fat Mass Index</td>
<td>0.819 0.387</td>
<td>&lt;0,001</td>
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</tbody>
</table>

[rBMI versus DXA data in total sample (n=133).]

Conclusions: reverse body mass index (rBMI) is an excellent tool to estimate Fat Mass in obese children and adolescents at different ages. It shows an excellent relationship with parameters of fat content measured by DEXA.

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An equation to estimate body fat percentage measured by DEXA in children and adolescents with overweight or obesity: a retrospective study

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Objectives and Study: Having in account that clinical problems because obesity are fat related, it is very important to estimate body fat. It presents difficulties in routine clinical practice because skinfolds are not as simple to measure or as reproducible as the weight and height of a child. For all these reasons, we aimed to develop and internally validate (intraclass correlation coefficient (ICC) and bootstrapping) a statistical model based on simple parameters (IBMI, sex and age) to predict body fat. Our goal was to obtain a simple tool that could be applied in clinical practice to assess adiposity in children and adolescents.

Method: We conducted a cross-sectional observational study in 416 obese children and adolescents aged 4-18 years (media 11.4 SD 2.8 years). All of them were attended in the Nutrition and Metabolism Unit at the San Joan University Hospital (Alicante, Spain). Our main outcome variables were body fat (% total body fat) and fat mass index (FMI, in kg/m2). These were measured by DEXA with a software able to obtain measurements for the total weight and percentage of body fat. These parameters were used as the reference standard measurements. As secondary variables we used iBMI (cm2/kg), sex (male or female) and age (years). This sample was randomly divided into two equal parts (n = 208). The first group was used to construct a predictive model (multivariable linear regression) and the second group was used to validate it.

Results: We analyzed a total sample of 416 children divided into two parts: 208 children in each group (construction and validation). Table 1 shows the descriptive analysis obtained for each group. Of note were a mean body fat of 43% and 11.7 kg/m² for FMI. No differences were observed in the groups, as all the p-values were greater than 0.05. For FMI the optimal model had a coefficient of determination of 0.86 and the formulas for the estimation of this parameter were (Table 2):
(A) Boys: $18.655 + 7.10^5 \cdot \text{BMI}^2 - 2936010 \cdot \text{BMI} + 0.112 \cdot \text{Age} - 0.018 \cdot \text{Age}^2$

(B) Girls: $18.655 + 7.10^5 \cdot \text{BMI}^2 - 2936010 \cdot \text{BMI}$

**Conclusion:** Body fat percentage and FMI measured by DXA can be accurately estimated in children and adolescents with overweight and obesity using our predictive models based on BMI, age and sex. Our models enable quick calculation of body fat percentage and FMI, thereby simplifying and reducing the use of resources in everyday clinical practice. We also highlight our methodology, which could be applied to obtain similar equations for the analyzed parameters.

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Frequency of vitamin and trace element disorders in children with intestinal failure

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Objectives and Study: Patients receiving long-term parenteral nutrition are at potential risk of vitamin and trace element deficiency or excess. We aimed to determine the frequency of these disorders in children with intestinal failure (IF) during the transition from home parenteral (PN) to enteral nutrition (EN).

Method: Prospective cohort study in children with IF during the transition from home PN to EN in an intestinal rehabilitation program between July 2015 and November 2017. Serum levels of iron, zinc, selenium, copper, chromium, manganese, aluminium, folate, 25-OH vitamin D, cobalamin and whole-blood thiamine levels were routinely monitored at 3-month intervals during the course of PN; this frequency was increased to once a month when deficiency was detected. Children that had at least three micronutrient measurements during the follow-up were included. All patients were receiving parenteral nutrition containing a fixed dose of vitamins and multi-trace element solution containing zinc, copper, chromium and manganese, and selenium separately. Median volume of diet intake (peptide-based or free amino formula) was 240 ml/day (interquartile range 40-455). No patient achieved full EN during the study period.

Results: Nine children aged 16.5 months (interquartile range 8-28) were included. The average follow-up was 9.8 months (interquartile range 4.2-22.6). Overall, 510 measurements were performed (average 48 measurements per patient). The most frequent cause of IF was necrotizing enterocolitis (55.5%). All patients had selenium deficiency on admission (9/9), which was corrected accordingly. Iron (5/9), copper (7/9) chromium (9/9) and 25-OH vitamin D (7/9) were the most common deficiencies during the follow-up, with all children having more than one micronutrient deficiency. No patient had cobalamin, folate or thiamine deficiency. Higher than normal serum levels of manganese (5/9), zinc (5/9), iron (8/9) and aluminium (persistently high in all patients) were detected during the study period.

Conclusion: Vitamin and trace element disorders are common in patients with IF during the transition from parenteral to enteral nutrition. Systematic monitoring is necessary to detect and manage deficiency, excess or toxicity over time.

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Decreased serum Nrg4 levels are associated with nonalcoholic fatty liver disease in obese children

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Objectives and Study: Neuregulin 4 (Nrg4), a newly identified adipokine secreted by brown adipose tissue, is hypothesized to play a crucial role in metabolism. The present study aimed to evaluate the association between serum Nrg4 levels and NAFLD in obese children.

Method: A total of 123 obese children were included in this study. Anthropometric and biochemical parameters were measured in all subjects. NAFLD was diagnosed using ultrasonography. The serum levels of Nrg4, leptin and adiponectin were measured by ELISA.

Results: NAFLD was identified in 58 obese children (47.2%). Serum Nrg4 levels were significantly lower in the NAFLD group (2.24 (1.20, 3.22) ng/ml) than in the control group (5.50 (2.45, 10.85) ng/ml) (p=0.014). Serum Nrg4 levels were negatively correlated with BMI (r=-0.222, p=0.014), waist circumference (r=-0.242, p=0.009), WHR (r=-0.194, p=0.037), WHtR (r=-0.263, p=0.005), TG (r=-0.268, p=0.003), FBI (r=-0.312, p=0.001), HOMA-IR (r=-0.322, p=0.001) and leptin (r=-0.182, p=0.044) but were positively correlated with FFM% (r=0.204, p=0.025) and HDL-c (r=0.222, p=0.015).

Furthermore, a multivariable logistic regression model indicated that increased Nrg4 levels were associated with reduced risk of NAFLD (β(SE)=-2.093(0.732), p=0.004). The receiver operating characteristic (ROC) curve analysis of the diagnostic value of using serum Nrg4 levels to differentiate NAFLD in obese children showed that the area under the curve (AUC) was 0.723; the cutoff for serum Nrg4 levels to have diagnostic value for predicting NAFLD in obese children was 3.39 ng/ml.

Conclusion: Nrg4 levels are inversely associated with NAFLD risk in obese Chinese children, suggesting that Nrg4 may protect against NAFLD development in obese children.

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Long-term efficacy and tolerance of statins in children

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Objectives and Study: Statins are commonly used in children with familial hypercholesterolemia to prevent cardiovascular risk in adulthood. Their efficacy and tolerance in the short-term (less than 2 years) are confirmed by many studies, but long-term data are very rare in children. The aim of our study was to evaluate the long-term efficacy and tolerance of statins in children and adolescents with familial hypercholesterolemia.

Method: Records of 131 children or adolescents treated with statins for familial hypercholesterolemia were analyzed retrospectively. The efficacy of the treatment was established by the percentage of children who managed to achieve LDL-cholesterol levels below 160 mg/dL during treatment and the decrease in LDL-cholesterol levels. Treatment tolerance was evaluated by the occurrence of clinical or biological side effects, regularity of height and weight growth, and pubertal development.

Results: Mean duration of treatment by statins was 4 years and 2 months. A mean decrease of 32% in LDL-cholesterol was observed (p<0.0001). The therapeutic target (LDL-cholesterol <160 mg/dL) was achieved in 67% of cases. Height and weight growth and sexual maturation were not affected by the treatment. Minor side effects were reported in 24 (18%) patients: 3 cases of clinically asymptomatic CPK (creatine phosphokinase) increase, 2 cases of CPK increase with muscular symptoms, 14 cases of myalgia without CPK increase, 3 cases of abdominal pain, 1 case of dysuria, and 1 case of diffuse pain. None of these side effects justified to discontinue the statin therapy, although a change of statin was required in 7 cases. This new statin was tolerated in all the cases. No patients experienced biological disturbance of the liver function during the course of the treatment.

Conclusion: The results of this large cohort confirm the long-term safety and efficacy of statin therapy in children with familial hypercholesterolemia.

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Classification of SBS according to anatomic features might help to determine prognosis and to define management strategies

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Short Bowel Syndrome (SBS) is the leading cause of Intestinal Failure (IF) in children. Classification of SBS into 3 types is new in pediatric SBS: type 1: end jejunostomy, type 2: jejuno-colic anastomosis and type 3: jejuno-ileal anastomosis. The aim of the study was to analyze the outcome according to this 3 types classification.

Study design: SBS pediatric patients referred to HPN between January 1st 2000 and December 31st 2015 were evaluated retrospectively. The bowel length, the level of PN dependency as assessed using the Non-protein energy intake/resting energy expenditure from Schofield formula (NPEI/REE), citrulline plasma levels, and outcome were analyzed

Results: A total of 156 children were included. In the type 1 group, none were weaned off until during the 16 years study period. In type 2, 80% of patients with &LT; 40 cm were PN-dependent after 4 years, versus 33% of patients with > 40 cm. In the SBS type 3 group, 61% of patients with &LT; 40 cm were PN-dependent after 4 years, versus 9% of patients with > 40 cm (p=0.003). Patients who have a length of remnant bowel > 40 cm have a weaning off relative risk of 5.8 (CI [3.1, 10.8], p&LT; 0.001), and those with the ICV present had a weaning off relative risk of 3.2 (CI [2.0, 5.3], p&LT; 0.001). Citrulline plasma levels have a negative correlation with the NPEI/REE, which differs according to anatomic features: in the SBS type 1 group this correlation is cor= -0.54 (p=0.03), in type 2 cor= -0.40 (p=0.045) and in type 3 cor= -0.61 (p=0.008).

Conclusion: HPN is a well-established and increasingly safe therapy for children with SBS-IF and should remain the first-line therapy for the long-term management. The objectives of an optimal management should be 1) favoring intestinal adaptation and oral skills by oral feeding. 2) maintaining normal growth, 3) preventing complications associated to IF and/or long-term PN. Classification into 3 types may predict outcome especially in terms of PN dependency duration in order to design adapted strategies including the use of GLP-2 analogs. No patient with an ostomy (type 1) was weaned off during the period and are potential candidates for intestinal transplantation unless GLP-2 analogs decrease significantly PN dependency.
Body composition correlates with laboratory parameters and disease severity in children with biliary atresia

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Objectives: Children with biliary atresia with failed Kasai suffer from chronic malnutrition. We aimed to assess the correlation of body composition with various laboratory parameters and the Pediatric End Stage Liver Disease (PELD) score.

Methods: Children with biliary atresia underwent full nutritional assessment by a dietitian that included dietary assessment and anthropometry measurements including weight and height, mid upper arm circumference, skin fold thickness and air displacement plethysmography (ADP). Mean percentage of fat mass (MPFM), fat free mass and fat mass index were measured by ADP. Laboratory tests were extracted from medical records and PELD Score for End-Stage Liver Disease was calculated. Correlations were calculated using Spearman test.

Results: A total of 34 tests were performed for 25 children including 14 females (56%). Median age was 15 weeks (range 4-56 weeks). Mean PELD score was 8 ±7.6. Mean z-score for height and weight were -1.7±1.58 and -2±1.22 respectively. Mean percentage of fat free mass and fat mass were 86.1%±5.1% and 3.8%±5.1% respectively. MPFM correlated positively with serum albumin (r=0.57) and INR (r=0.49) (p<0.05). Fat mass index correlated significantly only with INR (r=0.46, p&LT; 0.05). Fat free mass index correlated significantly with serum albumin (r=0.59, p&LT; 0.05). Negative correlation was observed between height z-score (r=-0.5), serum bilirubin (r=–0.52) and PELD score (p&LT; 0.05). Mid upper arm circumference (MUAC) correlated positively with serum albumin (r=0.76), weight z-score (r=0.58), height z-score (r=0.48) and negatively with serum bilirubin (r=–0.63) and PELD score (r=–0.66) (p&LT; 0.05). Skin fold thickness correlated with fat mass index measured by air displacement plethysmography (r=0.63, p&LT; 0.05).

Conclusions: In patients with biliary atresia, certain body composition measures are closely associated with laboratory parameters of disease severity and growth. Long term follow up is needed to find out whether they can serve as predictors of outcome.

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Nutritional status in newly diagnosed inflammatory bowel disease children: a prospective, comparison, single centre study

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Objectives and Study: The aims of this study were to characterize the incidence of malnutrition and micronutrients’ deficiencies in newly diagnosed IBD children and to compare with a group of healthy controls.

Method: We prospectively enrolled newly diagnosed IBD children coming to our referral center between September 2015 and October 2017. A group of healthy children referred to our primary care center for routine well-child visits was also recruited. Anthropometrics data [weight, height, body mass index (BMI)], triceps, biceps, subscapular and iliac crest skinfolds, waist, arm and wrist circumferences were evaluated at the enrollment. In addition, a qualitative and quantitative assessment of nutritional intake was performed through the administration of a validated food frequency questionnaire. Finally, the enrolled patients underwent the following blood panel: full blood count, ferritin, inflammatory indexes [C-reactive protein, erythrocyte sedimentation rate], albumin and other organ function markers, vitamins (A, B12, D, E and folate) and minerals (calcium, copper, phosphorus, magnesium, zinc, iron, sodium, potassium, clorum). For the IBD group data regarding demographic characteristics, disease localization according to Paris classification, disease activity indexes and ongoing therapy were also collected.

Results: Forty-six children affected by IBD [(CD:24 (52.1%), UC:22 (47.9%); median age: 12.8 yrs; range 2-17.6; M/F: 26/20] and 43 healthy controls [median age: 11.1 yrs; range 4.7-17; M/F: 21/22] were consecutively enrolled. IBD children showed significantly decreased mean values of BMI [17.5 versus (vs) 19.6 kg/m², p=0.008], biceps (5.9 vs 7.3 mm, p=0.02), subscapular (8.4 vs 11.5 mm, p=0.001) and iliac crest skinfolds (6.6 vs 8.2 mm, p=0.03), wrist (14.8 cm vs 15.7 cm, p=0.01) and waist circumferences (63.5 cm vs 67.5 cm, p=0.05) when compared to healthy patients. The mean daily caloric intake was not significantly different between IBD and healthy patients (1696.7 vs 1692.6 Kcal; p=0.9), although IBD children showed a significant decreased fibers intake respect to the controls (16.2 vs 24.3 g, p=0.03). When compared to the controls, IBD children had significantly lower calcium (9.2 vs 9.6 g/dl, p=0.001), clorum (103 vs 106 ug/dl, p=0.001) and iron blood levels (34.8 vs 89.9 mg/dl, p=0.0001). In addition, children with IBD showed a higher incidence of vitamin A [20/46 (43.4%) vs 6/43 (13.9%), p=0.002] and folate [14/46 (30.4%) vs 4/43 (9.3%), p=0.01] deficiencies. Vitamin D mean values were decreased in both IBD and healthy patients and were not significantly different (20.2 vs 24.2 ng/ml, p=0.1). In details, 7 out of 46 (15.2%) IBD children showed a vitamin D deficiency (&LT; 10 ng/ml) compared with 4 out of 43 controls (93%) (p=0.5), while 29/46 (63%) IBD children had vitamin D insufficiency (&LT; 30 ng/ml versus 26/43 controls (60.4%) (p=0.8). Only, 10/46 (21.7%) children with IBD and 13/43 (30.2%) controls had normal vitamin D values (>30 ng/ml) (p=0.8).

Conclusion: This study suggest that IBD children at diagnosis are at higher risk of malnutrition and may present micronutrients deficiencies. We identified a high percentage of vitamin D insufficiency and deficiency in both IBD and healthy children, suggesting that a revision of the current cut-offs should be envisaged.

Disclosure of interest: Annamaria Staiano served as investigator and member of advisory board for the following companies: D.M.G, Valeas, Angelini, Miltê, Danone, Nestlé, Sucampo, and Menarini. Erasmo Miele served as speaker, as investigator and member of advisory board for the following companies: Abbvie, Angelini, Bioprojet, Ferring, Menarini, Milte, and Valeas. The remaining authors have no conflict of interest to declare.

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Objectives and Study: The aim of the study was to assess the nutritional status of children referred for hematopoietic stem cell transplantation (HSCT) to a national reference centre for paediatric hematological disorders.

Design: Retrospective study of HSCT recipients &LT; 18 years referred between 2011 and 2016.

Method: Nutritional assessment was performed during the days prior to HSCT. General data collected included primary diagnosis, type of HSCT and development of graft-versus-host disease (GVHD). Nutritional data included z-scores for weight, height and body mass index (BMI), %standard weight, body composition parameters (according to bioimpedance analysis, Akern™ device) and resting energy expenditure (REE, indirect calorimetry, CCM™ device).

Results: 80 patients registered (37 male, 46.3%). Most frequent diagnosis (72.5%) were hematological malignancies (leukaemias, myelodysplastic syndromes, myeloproliferative syndromes), followed by immunodeficiencies (15%) and other diagnosis (12.5%). Mean age was 6.65±5.01 years (0.25-16.48). Children with immunodeficiencies were significantly younger at the time of HSCT (p&LT; 0.05). Anthropometry: mean weight z-score -0.48±1.5; mean height z-score -0.52±1.5; mean BMI z-score -0.23±1.4. There were 8.8% children with z-BMI ≤ -2 and 7.5% were overweight or obese. The group with immunodeficiencies showed the worst z-height and z-BMI values. There were significant differences in z-BMI between those who presented acute GVHD and those who did not (p&LT; 0.05). Body composition: 80% children showed body cell mass values &LT; 45% of lean body mass, indicating poor body protein status. There were no significant differences in body cell mass between those who presented acute GVHD and those who did not. Resting energy expenditure: indirect calorimetry was performed in 11 patients; mean REE was 52.8±28.4 Kcal/Kg of lean body mass.

Conclusion: Children with immunodeficiencies showed worse nutritional status, which is of special concern given their younger age. Despite BMI mostly showed normal values, body composition of these patients was negatively affected, as shown by reduced body cell mass. In this sample, body composition did not seem to be related to the development of GVHD.
A quantitative analysis of nutrition clinical studies conducted in paediatric population in Middle East region and its comparison with the world

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Objectives and Study: Middle East (ME) is the region with the highest percentage of children, currently, having about one-third of its population under age fifteen. The region’s child malnutrition rate is about 19% due to mainly poor health care. In this study, we aimed to quantify current status of nutrition clinical studies in paediatric population and to identify future potential and possible needs for clinical research in Middle East region.

Method: ClinicalTrials.gov was chosen as representative registry and was screened for clinical trial numbers. The numbers were analysed and compared according to region, country, age group, funder, activity status and condition.

Results: More than three fourths of all nutrition clinical trials in the world is currently being run in North America and Europe regions (76%, 6407 out of 8470) leaving only one fourth to the rest of the world (24%, 2063 out of 8470) (Figure 1A). Middle East is represented with 4% (313 out of 8470) of all nutrition trials with vast majority of the trials in this region being run in only three countries, Israel, Turkey and Iran (90%). Despite high relative percentage of paediatric population currently present in ME region, the clinical trial numbers run in paediatric population is also quite low and represent not more than total nutrition clinical trial involvement ratios (4%) (Figure 1B). There is only one phase 1 trial in the ME region, with majority of the trials being either in the later phases or observational, epidemiological. There is only one registry study in the region and there is no expanded access study. Poor nutrition or nutrition disorder studies dominate the condition spectrum (97 and 96 % respectively) with metabolic disorders, anaemia and allergy only playing a minor part. Interestingly, industry seems to be sponsoring less paediatric nutrition studies relative to total nutrition studies both in the world (14% vs 26%) and in ME region (16% vs 31%) compared to all other funders. While industry funded studies are being run in Israel (15%) and Turkey (31%), surprisingly, none of the studies in Iran is industry funded. There is only one paediatric nutrition study for each countries in Cyprus, Kuwait and Qatar and these studies all are funded by paediatric nutrition industry. In the world, the major clinical trial funder nutrition companies are Nestle, Mead Johnson, Abbott Nutrition and Danone-Nutricia. However, in ME region majority of the funding is coming from smaller regional or local companies while only Abbott Nutrition and Danone-Nutricia are currently sponsoring two and one studies in ME region respectively.

Conclusion: Significant majority of nutritional studies are being conducted in North America and Europe, with all the remaining regions including ME only comprising about one fourth of all studies. Despite its relatively high paediatric population and high prevalence of malnutrition, ME is not currently being well represented for clinical studies for paediatric population. Industrial funding for nutritional studies relies highly on the regional or local companies for ME with only limited participation of international nutrition companies. Results provide that there is a reasonable rationale and huge opportunity for ME region to be included in clinical research in paediatric population.
Regional distribution of all nutrition studies (panel 1A) and paediatric nutrition studies (panel 1B).

Disclosure of interest: Feza Kirbiyik is an employee of Nutricia Medical Department Turkey. Ali Evrim Doğan is an employee of Nutricia Medical Department Turkey.

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Cost effectiveness of Taurolock-Hep line lock by reducing Catheter Related Blood Stream Infections in children dependent on parenteral nutrition

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**Objectives and Study:** Patients on parenteral nutrition (PN) because of intestinal failure have high risk of Catheter Related Bloodstream Infection (CRBSI). These infections apart from being life threatening, may exacerbate the intestinal failure associated liver disease (IFALD) and often require removal of central venous catheters, minimising the availability of central venous access which is limited especially in very young infants. Preventing these infections is thus very imperative for the morbidity and mortality they cause which has been highlighted in a recent ESPGHAN position statement for the management of IFALD.

For prevention of CRBIs in children who receive parenteral nutrition current PN policy includes a bio-patch and para film for prevention of CRBSIs.

In order to reduce CRBIs, a new policy got approved by hospital committee for using prophylactic Taurolock-Hep in children receiving long term parenteral nutrition via a central venous line.

As a pilot to use it as standard line lock drug for patients on parenteral nutrition and with central lines, who have had 2 proven Catheter Related Blood Stream Infections (CRBSIs) within 6 months.

**Objectives:** To evaluate the effect of Taurolock Hep on CRBSI in children receiving long term parenteral nutrition via a central venous line and its cost effectiveness by undertaking prospective audit and reviewed for use it even after the 1st proven CRBSI episode.

**Methods:** Prospective audit to evaluate incidence of CRBSI over a period of 18 months (March 2016-Oct 2017). Results compared with retrospective data for similar period prior to introduction of Taurolock Hep i.e (Sept 2014-March 2016). Patients on TPN were identified from hospital database and electronic patient record system is used to look at episodes of CRBSI. We introduced standard recommended usage guidance for Taurolock™-Hep 100

**Results:** Taurolock was approved to be used in our trust in March 2016. Since then 10 TPN dependent patients received Taurolock-Hep as prophylactic line lock. Age range 19 months to 11 yr (median age 4yr 4 month).

We have observed that overall incidence of CRBSI over a period of 3 years were 37 episode. Prior to introduction of Taurolock Hep between Sept 2014-march 2016 there were 26 episode (70% ie 26/37), that led to approx 260 hospital admission bed days. This cost about £98800 (based on cost £380/day). While in post Taurolock period March 2016- Oct 2017 there were only 11 episode of CRBSI (30% ie 11/37) which required only about 110 days of hospital admission. The CRBSI rate has dropped significantly from 4.93 episode per 1000 catheter days to 2.01 episode per 1000 catheter days following usage of Taurolock (figure).

Main microorganism isolated was Klebsiella pneumonia, followed by Staph epidermidis, E Coli, candida.
[Effect of Taurolock Hep on CRBSI incidence]

**Conclusion:** There was a significant reduction in incidence of CRBSI after introduction of Taurolock line lock. Due to reduction in CRBSI none of the patients require line removal. By overall reduction in hospital stay trust made cost saving of about £57000. It also provided improved quality of life. We are now piloting introduced policy to use Taurolock Hep after 1st episode of CRBSI.

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Assessment of the nutritional status and quality of life of children with gastrostomy

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Objectives and Study: Gastrostomy feeding is indicated when oral feeding is not possible or insufficient, gastrointestinal function is at least partially preserved and when long-term enteral nutrition is expected. The aim of this study is to characterize patients to whom gastrostomy was performed in a tertiary hospital, to evaluate changes in its nutritional status and to know the caregivers' satisfaction regarding the procedure.

Method: The clinical features of children who had had a gastrostomy placed in the last five years (2012-2016) were reviewed. The following variables were analysed: demographic data, type of gastrostomy and related complications, anthropometric and data before and twelve month after the procedure. The Satisfaction Questionnaire with Gastrostomy Feeding (SAGA-8) was applied to evaluate caregivers' satisfaction.

Results: Gastrostomy was performed in 39 patients, 56% were boys and the median age was 4 years old (min 1 day - max 17 years). All patients have chronic diseases including neurologic disease (67%), gastrointestinal (18%), metabolic (5%), cromossopathy (2.5%) and chronic renal disease (2.5%). Percutaneous Endoscopic Gastrostomy was performed in 21% of the cases. The others had a Stamm surgery, since 72% also had a Nissen fundoplication at the same time. Enteral feeding was started 48 hours (median) after the gastrostomy placement and the median length of hospital stay was nine days. Early complications (< 30 days) were found in 36% of the patients and late complications (> 30 days) in 80%. Most of the complications were minor and included site infection (33.3%) and overgranulation (82.1%). Major complications including buried bumper happened in two patients and pneumoperitoneum in one patient. Eight children died due to events not related to the procedure. The weight for age was below the 3rd percentile in 73.0%, between the 3rd and 15th percentile in 13.5% and above the 15th percentile in 13.5%. Body mass index (BMI) was below the 3rd percentile in 55.6%. After the procedure, 63% of the patients still had the weight below the 3rd percentile but in 17.9% the weight improved. No differences were found regarding height and body mass index. Regarding the results of the SAGA-8 caregivers questionnaire: the total score range from 8 to 31, being the total average value of 28.32 (min.: 22 ; max.: 31) and 82% of the caregivers were very satisfied as for as feeding is concerned, 68% were pleased with the change that took place in their children's nutritional state and 82% would have accepted to place gastrostomy earlier if they had known about the benefits that gastrostomy has currently.

Conclusion: Minor complications were frequent but easy to solve, which confirms the safety of the procedure in either endoscopically or surgical procedure. Even though weight improvement was discrete, most of the caregivers were extremely satisfied with the subjective nutritional status improvement. The overall satisfaction rate regarding the gastrostomy was high, suggesting a better quality of life for the patient and his family. More information and earlier in the course of chronic diseases should be given to caregivers, this highlights the importance of Nutritional Support Teams.

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NUTRITION - Clinical nutrition

N-P-066

Influence of withholding early supplemental parenteral nutrition in undernourished critically ill children

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Objectives and Study: Children admitted to a paediatric intensive care unit (PICU) are often undernourished, which is associated with increased mortality and morbidity. Due to the lack of evidence concerning nutritional support in this group of children, there is debate about the optimal timing to start supplemental parenteral nutrition (PN). We investigated if withholding early PN is effective and safe in critically ill children who were undernourished on admission. Furthermore, we explored relations between change in weight during PICU stay and clinical outcomes, and the influence of PN hereon.

Method: This study is a post-hoc analysis of the PEPaNIC randomized controlled trial (1), in which critically ill children aged 0-17 years were studied. Nutritional status was assessed by performing measurements of weight and height upon admission and at discharge from the PICU. Undernourishment was defined as weight-for-age Z-score < -2 in children < 1 year, and body mass index-for-age Z-score &LT; -2 in older children. Primary outcomes were the incidence of nosocomial infections and length of PICU stay. Associations between the change in weight and clinical outcomes were investigated by use of logistic and Cox regression analyses, with and without PN as effect modifier.

Results: In total 289 of 1440 children (20%) were identified as being undernourished on admission, of whom 139 received early PN and 150 late PN. Baseline characteristics were similar in the two groups. There was an 11.0% reduction of nosocomial infections (p=0.02) and median 2 days shorter PICU stay (p=0.006) in the late PN group as compared to the early PN group. A deterioration of weight Z-score (assessed in 477 Dutch children) was associated with higher likelihood of acquiring new infection (β= -0.34, p &LT; 0.05), and a lower likelihood of earlier life discharge (β= 0.20, p &LT; 0.05), adjusted for baseline risk factors. Early administration of PN did not affect these relations. Also, early PN did not influence the change in weight Z-score (β= -0.10, p= 0.20).

Conclusion: Withholding PN during the first week of admission in acutely undernourished, critically ill children was clinically superior to supplementing PN. A deterioration of weight during PICU stay was associated with worse clinical outcomes, but administering PN early had no influence on this weight deterioration or its relation with clinical outcome.

References:

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Resting energy expenditure, body composition and micronutrient status in neurologically impaired children

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Objectives and Study: Cerebral palsy (CP) is the most common disability during childhood, and is frequently associated with feeding disorders leading to abnormal growth and body composition. In recent years, the attention to the nutritional management of children with CP has increased. This increased awareness should result in an improvement in the nutritional status of CP patients. We performed a global nutritional assessment in children with cerebral palsy (CP), evaluating body composition, resting energy expenditure (REE), and micronutrient status.

Method: We enrolled 22 children with CP (M 54.5%; mean age 11.4±2.75 years). In all subjects we evaluated weight and height z-scores (compared to national charts), gross motor function classification system (GMFCS), REE by indirect calorimetry and Schofield equations, body composition by bioimpedance analysis (BIA), skinfold thickness (SFT), mid-upper arm circumference (MUAC), and caloric intake by 24-h recall. Moreover, in 15 of these children we also dosed micronutrient plasma levels.

Results: In our study population, 2/22 subjects (9.1%) had a GMFCS-I and 20/22 (90.9%) had a GMFCS-V. Mean weight Z-score was -4.8±2.3, mean height Z-score was -2.9 ± 2.1, mean MUAC was 18.1±3.3 cm with values that were <10° ct in 18/22 subjects (82%), while mean triceps SFT was 6.7±3.4 mm with values <10° ct in 15/22 children (68%). Considering the nutritional intakes, mean caloric intake was 1156±359 Kcal/die, with inadequate daily intakes in 9/22 children (41%). Focusing on body composition evaluated by BIA, mean fat mass was 17.4±12.3%, mean fat free mass was 82.7±12.4%, and mean phase angle value was 4.4±1 with values that were normal (>6) only in 2/22 subjects (9%). In addition, mean REE measured by indirect calorimetry was 664±387 Kcal/die and was significantly lower compared to REE estimated by Schofield equation (mean 981±204 Kcal/die; p=0.001). Considering micronutrient status, we found that vitamin B12, A, E and copper levels were adequate in all the children, while mean vitamin D levels were 14.6±12.7 ng/ml and were inadequate in all the subjects. Mean folate levels were 6.7±11.3 ng/ml and mean zinc levels were 98.7±0.14 mcg/dl and were inadequate in 2/22 children (13.3%).

Conclusion: Despite the increased attention given to nutritional aspects, the majority of patients with CP is still malnourished and presents altered body composition, insufficient caloric intakes, and inadequate micronutrient status.

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Diagnostic work-up and micronutrient deficiencies in children with failure to thrive without underlying diseases

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Objectives and Study: Failure to thrive (FTT) is an interruption in the normal pattern of growth. There are limited studies about the benefit of routine laboratory investigations to identify the aetiology of FTT. The aim of this study was to evaluate the clinical characteristics, underlying aetiologies, diagnostic work-up and frequency of micronutrient deficiencies in children with FTT without underlying major medical diseases known to cause poor growth.

Method: The records of 1552 patients with E44/E45 codes (ICD-10) from January 2011 to January 2016 were reviewed retrospectively. Children with low weight for age (< 3rd percentile) were included. Children who had previously known chronic diseases, inadequate intake secondary to anatomic defects or inadequate absorption were excluded. 729 children (319 male) who met these criteria were recruited to the study. Age, gender, medical and dietary history, physical examination and laboratory findings at admission were recorded. Nutritional status of the cases was categorized according to the Waterlow classification. Laboratory tests including complete blood count, biochemical panel, acute phase reactants, thyroid screen test, celiac screen tests, urine analysis and culture, stool examination, chest X-ray, left hand X-ray, echocardiography, endoscopy, sweat test, parameters related to growth hormone, serum zinc, vitamin levels were each counted as 1 test. Based on dietary history, children without organic, psychiatric and behavioral pathology to explain FTT were defined as "purely" nutritional FTT due to inadequate intake.

Results: The mean age was 6.8±5.5 years. Of patients, 47.4% (346/729) were younger than 5 years. The overall malnutrition rate was 91.1% (670/729) (acute malnutrition 82.1%; chronic malnutrition 45.2%). Of children, 98.7% (720/729) had laboratory evaluation. A total of 5387 tests were performed with a median of 7 tests (range 1 to 15 ) per patient. Many abnormalities in blood, urine and stool tests and imaging studies were noted in 9% of patients, but it did not lead to any specific diagnosis. We found that 1.1% of laboratory tests, 0.4% of imaging studies and 83.8% of endoscopic findings and biopsy results led to specific diagnosis, equating to a total of 1.7% of diagnostic work-up leading to a diagnosis regarding the aetiology of FTT. The causes of FTT were inadequate nutrition (55.4%), psychiatric and behavioural disorders (17.2%), endocrinological disorders (9%), gastrointestinal diseases (7.9%), recurrent infections (6.4%) and cardiac disorders (0.01%). Zinc and vitamin D deficiencies were the most common micronutrient deficiencies. No difference was observed in the frequency of micronutrient deficiencies between children with acute and chronic malnutrition.

Conclusion: We showed that the most common etiology of FTT without any major medical disease at presentation is "purely" nutritional FTT due to inadequate caloric intake, and extensive diagnostic work-up is rarely helpful to reveal the aetiology if there is no clinical suspicion. Besides organic causes of FTT, physicians should also focus on behavioral, developmental, psychosocial and environmental risk factors for the development of FTT.

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Assessment of Cow’s milk-related symptom scoring awareness tool in Turkish infants

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Objectives and Study: Cow's milk protein allergy (CMPA) may present with common non-specific symptoms (regurgitation, infantile colic or constipation) which may cause delay and difficulty in the diagnosis and treatment. Cow's Milk-related Symptom Score (CoMISS) is an awareness tool for cow's milk-related symptoms which includes the scoring of gastrointestinal (GI), dermatological and respiratory symptoms, and general manifestations. A symptom based score (SBS) of ≥12 has been suggested as a cut-off value to select the infants who are at risk of underlying CMPA. In this prospective study we aimed to evaluate the usefulness of CoMISS for the diagnostic approach to CMPA.

Method: This study included 2-weeks to 12-months-old infants who were admitted to our hospital between September 2015- March 2017 with GI, respiratory and dermatological symptoms and who were scored ≥12 SBS when evaluated by CoMISS. Symptoms, signs, physical examination findings and laboratory findings (complete blood count, erythrocyte sedimentation rate, albumin level, stool examination, IgE and cow's milk specific IgE (CM-sIgE) and Skin prick test (SPT) were recorded. Elimination diet (diet for the mother for breast fed, extensively hydrolysed formula and amino acid formula to formula-fed infants as a stepwise approach for non-responders) was started and CoMISS score was repeated in all infants after 4 weeks. Challenge test was performed to infants in whom a reduction of ≥ 3 points were recorded after the elimination diet. The infants unresponsive to elimination diet or negative to challenge test were defined as CMPA⁻; while infants with a positive challenge test were defined as CMPA⁺.

Results: A total of 194 infants had ≥12 SBS, however 168 infants (median age 3.4, range 2-11 months) completed the study period. CMPA was diagnosed in 54.2% (91/168) of these infants after the challenge test. The mean score at inclusion was 13.60±1.99 (range 12-22) and it was not statistically different in CMPA⁺ and CMPA⁻ group (p=0.15). The SBS decreased ≥3 points in 89.9% of the infants after elimination diet, however reduction of SBS was statistically significant in CMPA⁺ group (p=0.022).While mean crying and regurgitation scores of CMPA⁻ infants were significantly higher than that of CMPA⁺ infants (p=0.031 and p < 0.001 respectively), mean atopic dermatitis score was higher in CMPA⁺ infants (p=0.001). Familial history of allergy was also more prevalent in this group. Mean total IgE and the number of infants with positive CM-sIgE were significantly higher in CMPA⁺ infants (p=0.006 and p < 0.001 respectively). Of the CMPA⁺ 91 infants, 22 (24.4%) had positive CM-sIgE. SPT was positive in 20/71of CMPA⁺ patients.

Conclusion: We showed that by using CoMISS, 54.2% of infants with ≥12 SBS presenting with non-specific GIS symptoms such as regurgitation, infantile colic or constipation, had underlying CMPA. CoMISS is a simple and useful tool to screen infants for potential risk of CMPA who present with non-specific symptoms. A significant reduction of SBS after elimination diet helps to recognise the infants with CMPA.

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Comparison of nutritional status and dietary intake in school-aged children living in rural and urban area

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Objectives and Study: Dietary habits and the prevalence of obesity may differ significantly between regions of the same country. In order to prevent diet related health problems, it is important to monitor dietary intake patterns between different regions. Differences in nutritional status and dietary habits between urban and rural residents have been reported in some studies, although results have been mixed. Our aim was to explore the difference in nutritional status and dietary intakes between 12-15 year old subjects living in one urban (Zagreb) and one rural (Sinj) area of Croatia.

Method: A validated Food Frequency Questionnaire (FFQ) was used to assess dietary intake. For each participant body weight (BW), body height (BH), middle upper arm circumference (MUAC), triceps skinfold (TSF) and subscapular skinfold (SSF) thickness were measured. Bioelectrical impedance was used to estimate their body composition. Z-scores for each participant were estimated by the Growth Analyser software (BW/age, BH/age, BW/BH, MUAC/age, TSF/age, SSF/age). Statistical analysis was performed using SPSS 19.0 (Chicago, IL) statistical software.

Results: There was overall 120 children included; 49 (41%) in Zagreb and 71 (59%) in Sinj; 68 (57%) female and 52 (43%) male; mean age 13.5 years (range 12-15 years).

After adjusting for age there was significant difference in cholesterol consumption between Zagreb and Sinj (mean 235.3 g ± 135 SD vs 323.9 g ± 217.7 SD; p=0.007), water (mean 1326.1 g ± 563.5 SD vs 1527.3 g ± 523.4 SD; p=0.037) and animal protein consumption (mean 98.7 g ± 39.9 SD vs 107.7 g ± 36.3 SD; p=0.029). For other parts in FFQ there was no significant difference.

Overall, protein intake was above 200% of Recommended Dietary Allowances (RDA) for both regions. The proportion of energy coming from fat was above Acceptable Macronutrient Distribution Range (39.5% for Sinj and 38.6% for Zagreb).

In anthropometric parameters there was significant difference after adjusting for age and gender between Zagreb and Sinj in strength of both hands ((right hand: mean 21.7 kg ± 6.7 SD vs 28.7 kg± 9.4 SD p=0.001) and (left hand: mean 19.7 kg ± 6.3 SD vs 25.6 kg± 8.1 SD p=0.001)). For other anthropometric measures there was no difference.

On average, 20.8 % (n=25) of children from Zagreb and Sinj were overweight and 6.7 % (n=8) were obese. There was no difference in the proportion of undernourished, well-nourished, overweight and obese patients between two centers (p=0.63).

Conclusion: The living area doesn't appear to be an important factor influencing nutritional intake and nutritional status of 12 to 15 year old children. The higher intake of cholesterol in rural area could be explained by higher animal protein intake. The high prevalence of obesity and overweight in both areas are of concern. Results of this study indicate that inappropriate dietary patterns are prevalent in both rural and urban areas of Croatia and that nutritional interventions should be directed on both regions. This study represents preliminary results of larger pantients' cohort and should be, therefore, interpreted with caution due to small sample size.

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Analysis of the pediatric home enteral nutrition in Campania region: implementation rates and observed trends during the past 10 years

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Objectives and Study: The home enteral nutrition (HEN) provides nutritional support to children with chronic diseases who are nutritionally compromised and allows them to be discharged more quickly from hospitals. Since 2007, in Campania region was identified a pediatric Artificial Nutrition Referred Center with the objective of optimizing pediatric HEN and gathering information about practices in Campania region. The aim of our study is to update the rate of HEN in Campania region (Southern Italy) and pediatric patient clinical characteristics as experience of Artificial Pediatric Nutrition Unit from 2007 to 2017.

Method: A database including all pediatric patients followed up by HEN Unit of Federico II was used. Chi-square test was used for statistical analysis.

Results: The number of HEN increased during the past 10 years. Actually, many children with chronic illness benefit from HEN, mainly those suffering from neurological diseases 57.7%, 12.8% digestive diseases, 11.5% eating disorders, 5.1% inborn error of the metabolism and 12.8% other diseases. The prevalence of neuro-genetic disorders significantly increased in the last 2 years compared with the previous two years (p=0.0166) or with the previous five years (p=0.0003). On the contrary, the prevalence of allergic diseases significantly decreased in the last 5 years compared with the previous five years (p<0.0001) and no patients were followed by our unit in the last 2 years. HEN in children with eating disorders was stable during the 10 years and did not exceed the 11.5% of prescriptions. Type of feeding is oral for 64.4% of children in HEN and 35.6% by tube feeding of which Percutaneous Endoscopic Gastrostomy (PEG) and Nasogastric tube (NG) represent 92.3% and 7.7% of route of delivery, respectively.

Conclusion: Total number of patients with HEN are increased more than 7-fold during the past 10 years of observation. A significant change was observed related to the increase of neuro-genetic disorders and a decreased of allergic disease. The oral route represents the main type of feeding and all patients changed from homemade food to enteral formula.

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**NUTRITION - Clinical nutrition**

N-P-072

**Iodine and iron status in paediatric patients receiving long-term home parenteral nutrition**

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**Objectives and Study:** To assess iodine and iron status in Paediatric patients receiving long-term home parenteral nutrition (HPN) age 2-18 years and compare this to a group of healthy children.

**Method:** An observational cross-sectional study was performed at Oslo University Hospital and at the Department of Nutrition, University of Oslo from January 2017 to May 2017. Nineteen HPN children and 35 healthy children, age two to 18 years, were included. Intake of iodine and iron were assessed by a four-day food record, and enteral and parenteral provision recorded. Two spot urine samples from each subject were analysed for iodine concentration (UIC) and creatinine. Blood samples were analysed for hemoglobin, ferritin, and transferrin receptor levels to assess iron status.

**Results:** Mean age in the HPN patients and healthy children, was ten and nine years, respectively. Median intake of iodine was lower than the recommended daily intake (RDI) in both HPN patients and healthy children, (93 % vs. 80 % of RDI). Median parenteral iodine supply was above the ESPGHAN recommendation, yet the HPN patients had a median UIC of 89 µg/L, indicating insufficient iodine status. More than half of the HPN children had UIC values under the cut-off for sufficiency. This may indicate that the ESPGHAN recommendation for pediatric HPN patients is too low. The healthy children had sufficient iodine status according to median UIC (130 µg/L), however 59 % had insufficient iodine status when corrected for creatinine excretion. Iron provision among HPN patients was significantly lower than iron intake in the healthy children (54 % of RDI vs. 97 % of RDI, p=0.004). All HPN patients had parenteral iron provision below ESPGHAN recommendation. The prevalence of anemia was significantly higher among HPN patients compared to healthy children (42 % vs. 12 %, p=0.016).

**Conclusion:** The study indicates insufficient iodine and iron status among pediatric HPN patients. Further research is needed to confirm our findings.

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Assessing the utility of anthropometric measurements in determining body composition among children and adolescents with inflammatory bowel disease

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Objectives and Study: Anthropometric measurements, such as mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSFT), are used to assess body composition clinically. They are inexpensive and easy to measure, however, they can be inaccurate, particularly in overweight/obese patients. Air displacement plethysmography (BOD POD®) is an operator independent approach to accurately determining body composition. The objectives of this study were to assess the body composition of paediatric inflammatory bowel disease (IBD) patients initiating Infliximab (IFX) therapy using BOD POD®, and to ascertain the accuracy of traditionally used anthropometric measurements by comparison.

Method: All out-patients at the Hospital for Sick Children (Toronto, Canada) receiving induction IFX therapy from February 2017 onwards were eligible. Body composition was assessed via BOD POD® and skinfold measurements. Two trained clinical dietitians obtained MUAC and TSFT measurements (3 per patient, averaged) using standardized approaches. MUAC and TSFT were used to calculate arm fat area (AFA) and arm muscle area (AMA), which were converted into z-scores. BOD POD® output was categorized as ultra-lean, lean (includes moderately lean) and excess fat. Spearman correlations, Mann-Whitney test and Intra-class correlations were applied when appropriate.

Results: Twenty-five (64% male; 54% Crohn’s, 38% Ulcerative Colitis, 8% IBD-U) patients were included. Median age was 15 years (13-16). Based on BOD POD® classifications, the majority of patients had excess fat (60%), with the remainder being lean or extra lean (32% and 8%, respectively). Body mass index (BMI), AFA, and AMA z-scores for all BOD POD® classifications were within normal limits (Table 1). There was no significant difference between median AFA and AMA z-scores among patients classified as ultra-lean or lean, whereas among patients classified to have excess fat, arm fat was significantly greater than arm muscle (median AFA z-score vs. median AMA z-score, p=0.015). There was significant agreement between MUAC and TSFT between clinicians (r=0.995 and 0.982, respectively; p<0.05). There was significant agreement for the three TSFT measurements obtained by each clinician, rater 1 and 2 (r=0.999 and 0.998, respectively; p<0.05).

Conclusion: The majority of stable paediatric out-patients with IBD receiving anti-TNF induction have excess fat. BMI is an inaccurate measure of adiposity in this patient cohort, as are AFA and AMA, despite evidence that well-trained clinicians can obtain reliable MUAC and TSFT measurements. Clinicians caring for stable patients with IBD should be aware that this population is at risk for excess fat and as such a healthy lifestyle should be encouraged to help prevent/treat excess adiposity.

<table>
<thead>
<tr>
<th>BOD POD Classification</th>
<th>BMI (z-score; IQR)</th>
<th>AFA (z-score; IQR)</th>
<th>AMA (z-score; IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-lean (n=2)</td>
<td>-0.77 (-0.83, -0.71)</td>
<td>-1.12 (-1.78, -0.46)</td>
<td>-0.91 (-0.95, -0.86)</td>
</tr>
<tr>
<td>Lean (n=8)</td>
<td>-0.83 (-1.58, -0.09)</td>
<td>-0.25 (-1.07, 0.53)</td>
<td>-1.07 (-1.29, -0.60)</td>
</tr>
<tr>
<td>Excess Fat (n=15)</td>
<td>0.13 (-0.20, 1.51)</td>
<td>0.47 (0.26, 1.20)</td>
<td>-0.67 (-1.47, 0.65)</td>
</tr>
</tbody>
</table>

[Z-score medians for anthropometric measures]
Audit to assess the monitoring of nutritional status in children with severe disability on home enteral tube feeding (HETF)

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Objectives and Study: A retrospective analysis was performed looking at all children in the Southampton region on HETF, exclusively enterally fed with severe neurodisability. The aim of this study was to evaluate the adequacy of nutritional intake and nutritional assessment in children with neurodisability on home enteral tube feeding (HETF).

Method: Children with severe neurodisability (GMFCS 4 or 5) between 2-18 years of age on exclusive home enteral tube feeding (HETF) were selected. The list of patients on HETF was obtained from the records of companies providing feeds and suitable children identified. Children having oral tasters were included but children on blended diets were excluded. Electronic patient records were searched for information regarding demographic data, diagnosis, date of dietetic review, type and amount of feed and anthropometric measurements. All feeding plans were analysed and compared to the recognised reference values: Estimated Average Requirement (EAR) and the Reference Nutrient Intake (RNI).

Results: A total of 27 patients (13 males) with a median age of 8 years, were included. The commonest aetiological cause of neurodisability was cerebral palsy. Over a 12 month period all except 1 patient had their weight recorded but length was recorded in only 12 (44%) patients and 4 (15%) had their micronutrient status checked. In the last 6 months 8 patients (30%) had no documented dietetic review and weight was not recorded for 6 (22%) patients. Anthropometric measures other than weight and height were not recorded for any patient.

The median weight for age z-score was -0.63 {-7.51, 1.4} and it was below -2 Standard Deviation (S.D.) in 12 (44%) cases. BMI could only be calculated for 12 patients where length was available and was &LT; -2 SD for 3 and > 2SD for further 2 cases (Median -1.14 range -3.92, 2.36). For the 12 cases with WFA &LT; 2 S.D. BMI was recorded in only 6 and was &LT; -2 S.D. in 2. These children only received a median of 46% (18.9 - 87.1%) of the estimated calorie requirements and 93% (30.3 - 197%) of estimated protein requirements. The feed provided 59% of sodium, 51% potassium, 233% vitamin E and 314% vitamin C. All other micronutrients were within RNI range.

Conclusion: This study highlights the challenges in assessment and management of nutrition in children with neurodisability. Weight was the most frequently measured anthropometric parameter and was recorded in 26/27 patients. Length which can be difficult to measure and may need proxy measurements was recorded in less than half of the patients and no other anthropometric measures were recorded. Despite being completely dependent on artificial formulas the micronutrient status was checked only in 4/27 patients. Weight for age was less than -2 S.D. in nearly half of the patients and BMI, which could only be calculated for 12 patients, was out of range for 5. This therefore suggests we are not meeting their energy requirements. On average the feeding regimes provided 50% of estimated calorie requirements. The nutritional adequacy of feeds could not be accurately assessed, as a complete nutritional assessment was not possible in over half the patients.

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A register-based study on malnutrition risk screening and the prevalence of malnutrition in a tertiary hospital in Finland

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Objectives and Study: International as well as national guidelines instruct that nutrition risk screening should be done in all inpatients on the second day of hospital stay at the latest. We sought to study the prevalence of malnutrition risk scores and malnutrition in Finnish paediatric patients in all Helsinki and Uusimaa hospital district hospitals.

Method: During one day in 2015, 2016 and 2017 each, the malnutrition risk scores with the STRONGKids screening tool as well as the prevalence of malnutrition were studied in all paediatric wards. In 2017, we expanded the screening to include all ambulatory visits during the study day. Nurses conducted the malnutrition risk screening and measured the children's height and weight and recorded the information in electronic hospital database charts, where the information was drawn from by data administration. Data handling and statistical analysis were carried out with IBM SPSS Statistics version 24 (Chi square, Fisher's exact, Kruskal-Wallis and Mann-Whitney U-tests as appropriate).

Results: Altogether 696 patients were screened: in 2015, 162; in 2016, 133; and in 2017, 103 paediatric inpatients as well as in 2017, 298 children attending the outpatient clinics. There was no difference in malnutrition risk scores between the study years (p = 0.894), but more inpatients than outpatients had high risk scores (p < 0.001; Table). The highest portions of high risk patients were among hematological (32.4%), nephrological (12.5%), gastroenterological (12.5%) and cardiac (11.8%) patients. Of the children with weight-to-height < -20%, 3 (9.1%) were classified as having high, 12 (6.5%) moderate and 2 (0.6%) low risk for malnutrition.

The median (interquartile range, IQR) length of hospital stay was 2 (1 - 7) days for low, 4 (1.5 - 11) days for medium and 8.5 (2.25 - 30.25) days for high risk patients (p= 0.001). The median (IQR) costs were 4470 (1790 - 11780) € for low, 6240 (2710 - 23700) € for moderate and 14200 (2640 - 84190) € for high-risk inpatients (p < 0.001) and 230 (190 - 340) € for low, 290 (220 - 550) € for moderate and 590 (160 - 1370) € for high risk outpatients (p = 0.011), respectively. The costs or length of hospital stay did not differ between those whose weight-to-height was below or above -20% nor in those with height SD below or above -2 SD.

Despite instructions, the height and weight was not measured in all children, partly due to lack of equipment. Of outpatients, 92.6% and of inpatients, 75.1% had both measurements taken within a month from the nutrition risk screening. Height and/or weight measurements were missing from seven (17.5%) children with high risk for malnutrition; they were all inpatients. Of moderate risk patients, 40 (32.1%) inpatients and 4 (7.1%) outpatients had no record of weight and height measurements.

<table>
<thead>
<tr>
<th>Malnutrition risk scores*</th>
<th>Prevalence of malnutrition**</th>
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<tbody>
<tr>
<td></td>
<td>Weight-to-height &lt; -20%</td>
</tr>
<tr>
<td>Inpatients, n (%)</td>
<td>188 (47.2%)</td>
</tr>
<tr>
<td>Outpatients, n (%)</td>
<td>239 (80.2%)</td>
</tr>
<tr>
<td>Total n (%)</td>
<td>427 (61.4%)</td>
</tr>
</tbody>
</table>

* p < 0.05 for difference between inpatients and outpatients **Malnutrition could be determined only in those with both height and weight measurements available; ISO-BMI is calculated only those aged 2 years and above.

[Prevalence of malnutrition risk and malnutrition]
Conclusion: Approximately one in ten inpatients were at high risk, whereas only one in hundred outpatients were at high risk for malnutrition. The prevalence of acute malnutrition in inpatients was low (3.3%), while stunting was more common (19.4%). Continuous training of the nurses is needed for proper use of the malnutrition risk screening tool. The possibility to measure the heights and weights of the children should be ensured also for inpatients with the availability of appropriate equipment.

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Should we eliminate FODMAPs from diet in IBS patients? A systematic review in adult and paediatric population

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Objectives and Study: Despite the rising of the FGIDs’ incidence in the last years, the etiopathogenesis of Functional Gastrointestinal Disorders (FGIDs) remains unclear. The diet seems to play an important role in these disorders. Indeed, at least two thirds of adult patients with Irritable Bowel Syndrome (IBS) and of children with FGIDs perceive their GI symptoms to be food-related. In particular, in the last years, more interest has been focused in the low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyol (FODMAP) diet. However, the evidence of its effectiveness, especially in paediatric age, is limited. The aim of our study was to provide a systematic review of the literature on the efficacy of FODMAPs diet in reducing symptoms related to FGIDs.

Method: Cochrane Library, MEDLINE (via Pubmed), and EMBASE databases from inception to June 2017 were searched, with the following search terms: "FODMAP", "FODMAPs", "fermentable oligosaccharides, disaccharides and monosaccharides and polyols", "fermentable, poorly absorbed, short chain carbohydrates", "lactose free-diet" and "functional gastrointestinal disorders", "functional abdominal pain", "recurrent abdominal pain", "irritable bowel syndrome". We included randomized controlled trials (RCTs), prospective and retrospective studies, systematic reviews and meta-analysis, reporting the efficacy of the FODMAPs diet intervention in FGIDs patients.

Results: Nineteen studies were eligible. FODMAPs were beneficial in 12/13 intervention trials. Low FODMAPs diet improves overall GI symptoms, especially abdominal pain and bloating. A low FODMAP diet resulted also in an improvement of stool frequency and consistency in all papers reviewed expect one. In paediatric age, only one study exist comparing the FODMAP diet with a traditional diet in IBS children, showing fewer episodes of abdominal pain among children on FODMAP diet respect to children on traditional diet [1.1 ± 0.2 vs. 1.7 ± 0.4 pain episodes per day, respectively; P &LT; 0.05]. No effect was found for the lactose free diet whilst fructose-restricted diet was effective in 3/4 studies. The duration of the intervention was very different among the studies, ranging from 2 days to 16 months, and from 3 and 9 weeks for the RCTs. The majority of the trials presented differences in symptoms scoring scales, diet, food diaries, and food frequencies questionnaire.

Conclusion: In conclusion, this systematic review shows that restriction of FODMAPs may be an effective dietary intervention for reducing IBS symptoms in adults. In children, even if data are very promising, just one randomized double-blind study exists and further studies are needed to better clarify the role of FODMAP. The current evidence does not support the use of a lactose restricted diet in children with IBS, while further studies are needed to establish the role of the fructose restricted diet in the IBS symptoms’ relief in children.

Disclosure of interest: E. Miele has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbvie, Angelini, Ferring, Humana, Milté, Takeda; S. Salvatore has participated as consultant and/or speaker for Deca, IMS-Health, Danone, Nestlé, Menarini; A. Staiano has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for D.M.G, Valeas, Angelini, Milté, Danone, Nestlé, Sucampo, Menarini

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Increased Incidence of copper deficiency in infants with intestinal failure and parenteral nutrition dependence who develop cholestasis

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2 Dell Medical School, University of Texas at Austin, Austin, United States

Objectives and Study: In parenteral nutrition (PN)-dependent cholestatic infants, the amount of copper (Cu) in PN is often limited due to the risk of Cu toxicity. Cu deficiency can, however, lead to bone disease, anemia, and growth failure. We aimed to evaluate conjugated bilirubin (CB) levels, Cu supplementation, and serum Cu levels in PN-dependent infants with intestinal failure.

Method: Infants were divided into two groups based on their highest CB levels (< 2 mg/dL: non-cholestasis, n = 12, and ≥ 2 mg/dL: cholestasis, n = 23). The amount of Cu supplementation and the incidence of Cu deficiency (serum Cu levels ≤ 50 mcg/dL) were then compared. The association between the amount of Cu supplementation, CB, and serum Cu levels were also determined.

Results: Patients with non-cholestasis received higher Cu intakes than those with cholestasis (median 18.6 (20, 8.9) vs. 8.6 (20, 5.7) mcg/kg/d, P = 0.195). Although, there was no statistically significant difference of Cu supplementation between both groups, the incidence of Cu deficiency in cholestatic infants was significantly higher than that in non-cholestatic infants (52.2% vs. 16.7%, P = 0.042) (Figure 1). Significant association (R² = 0.192, P = 0.009) and negative correlation (r = -0.431, P = 0.01) between CB and Cu levels were demonstrated.

Conclusions: Serum Cu levels were low in infants with intestinal failure and PN dependence who developed cholestasis. This is probably due to greater reduction in parenteral Cu supplementation. Our findings suggest that Cu deficiency may be more common than previously reported. However, CB and serum Cu levels were measured at various intervals. Therefore, a causal relationship between Cu supplementation dose and Cu deficiency cannot be clearly inferred. In the future, a prospective study with larger sample size should be conducted using a systematic Cu dosing protocol in order to determine the optimal strategy for Cu supplementation in cholestatic patients receiving long-term PN. Regular monitoring of serum Cu levels should be obtained for optimal dose adjustment in PN-dependent cholestatic infants.

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**Risk factors of parenteral nutrition-associated cholestasis in very low birth weight infants: a 16-year dual-center experience**

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**Objectives and Study:** Very low birth weight (VLBW) infants often need long-term parenteral nutrition (PN). Parenteral nutrition-associated cholestasis (PNAC) is one of the most challenging complications of prolonged PN. The aim of this study was to explore risk factors associated with PNAC in VLBW infants.

**Method:** VLBW infants (n = 387) receiving PN for at least 14 days were enrolled in a retrospective dual-center study, and divided into two groups based on PN years: group A (2000-2007, n = 53) and group B (2008-2015, n = 334). A case-control study was conducted comparing infants with PNAC and without PNAC.

**Results:** In total, 26 (6.7%) VLBW infants developed PNAC. Logistic regression showed that prolonged duration of PN (≥43 days) (OR 3.32, 95%CI 1.07-10.278, p 0.037) was an independent risk factor of PNAC.

**Conclusion:** For VLBW infants, prolonged duration of PN (≥43 days) is a risk factor for the development of PNAC. PNAC may be prevented by weaning VLBW infants off PN as soon as possible.

**Disclosure of interest:** Nan Wang and Weihui Yan contributed equally to this work and share the first authorship. Corresponding author: Wei Cai email: caiw204@sjtu.edu.cn. Ying Wang email: wangying02@xinhuamed.com.cn

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Objectives and Study: Anorexia nervosa (AN) is a condition of self-induced weight loss that in children and adolescents can result in numerous metabolic complication. Dysmotility is one of the most frequent gastrointestinal disturbance and often difficult to manage. Intestinal microbiota plays an important role in gut motility and thus probiotics are commonly recommended for management of constipation. The data on the probiotic use in patients with AN and constipation are scarce. There is only few studies about the role of the probiotics in patient with AN, and all of them are on the adult population. Since there is no paediatric study, we chose Lactobacillus reuteri DSM 17938 to investigate its role in nutritional recovery and treatment of constipation in children and adolescents with AN.

Method: In total, our randomised, double blind, placebo controlled study included 31 female paediatric patients with AN and constipation (according to APA DSM-V and Rome III criteria) referred to gastroenterologist at the Department of Pediatric Gastroenterology, Hepatology and Nutrition, University Hospital Sestre milosrdnice Zagreb. Patients, randomly assigned into the L. reuteri or Placebo group after being hospitalized, were taking L. reuteri or Placebo for 3 months, along with the conventional nutritional rehabilitation and additional enteral nutrition. They were regularly measured and followed 6 months after initiation of treatment. The primary outcome was relief of constipation (drop-out from Rome III criteria), assessed after 3 months. Secondary outcomes were normalization of body weight (Z-score for BMI less than -1.5, or normalisation of menstrual cycle), normalisation of stool frequency and consistency, weight gain and recovery of malnutrition regarding bone density and vitamin D3 serum levels, 6 months after initiation of treatment.

Results: In L.reuteri group 13/15 patients (87%), and 10/16 patients (63%) from Placebo group were relieved of constipation after 3 months. There was no statistically significant difference between the two groups (p-value 0.22). After 6 months, 14/15 patients (93%) in L.reuteri group and 10/16 (63%) in Placebo group achieved normalization of body weight (p-value 0.04). There was a statistically significant difference between the two groups considering the stool frequency (per week) after 6 months (p-value 0.04). Although there was a positive trend considering the bone density recovery and vitamin D3 levels after 6 months, it was no significant which can be explained by the short period of observation.

Conclusion: This is the first study with Lactobacillus reuteri DSM 17938 in children and adolescents with AN and constipation. L.reuteri DSM 17938 was more effective than placebo in improving bowel movements and normalization of body weight in children and adolescents with AN. L.reuteri DSM 17938 showed positive trend considering the bone density recovery and vitamin D3 levels after 6 month. On the basis of our results probiotics can potentially serve as simple and safe treatment for constipation in AN.

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Natural history of paediatric intestinal failure: a systematic review and meta-analysis

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Objectives and Study: Intestinal failure (IF) is a major cause of morbidity and mortality in children, and its prevalence is increasing due to improved neonatal care. To date, cohort studies have primarily been from single centres and of small size. Therefore, we aimed to describe the natural history of clinical outcomes in childhood-onset IF.

Method: A MEDLINE search was performed using terms including: 'intestinal failure', 'paediatric', 'parenteral nutrition (PN)', 'liver disease', and 'IFALD'. The inclusion criteria were: IF before 18 years, reporting of clinical outcomes (e.g. liver failure, death, transplant), and >12 months follow-up. IF was defined as PN dependence for at least two months, or according to the authors' own definition. Studies were grouped by patient cohort: IF; IFALD; previous bowel lengthening procedure; and evaluated for intestinal transplant. Risk of bias was assessed using the ROBINS-I tool.

Results: 1584 articles were screened and 184 were included with a total of 9806 patients, sub-divided into 7371 with IF, 852 with IFALD, 681 with IF and bowel lengthening, and 902 being evaluated for intestinal transplant (ITx). Mortality was highest in the IFALD group at 0.23 (95% CI 0.15-0.31) at 28.7 months, and similar for the other 3 groups: 0.14-0.16 (95% CI 0.13-0.20) at 47-59 months. Liver-related mortality was more common in those with IFALD (50% of deaths) and those evaluated for small bowel transplant (56% of deaths), compared to 36% of deaths in the IF group. Sepsis was the second leading cause of mortality in all groups (25.0-34.6% of deaths). Patients evaluated for ITx were the most likely to develop IFALD (54.1%) and liver failure (17.9%) compared to the other non-IFALD groups (32.4-46.1% for IFALD and 7.5-11.3% for liver failure). The IFALD group had the overall highest rate of liver failure (44.2%) compared to 7.5% in IF (p< 0.0001).

The proportion of patients reaching enteral autonomy was significantly lower in patients evaluated for ITx (21.1%), but was similar between the other 3 groups (54.3%-57.8%, p< 0.0001 compared to IF group, p=0.0006 compared to bowel lengthening group, and p=0.0042 compared to IFALD group). Mean septic episodes per patient were higher in the evaluated for ITx group compared to the IF group (4.94 vs 2.23). Patients with IFALD were born at a younger gestational age (32.4 vs. 33.6 weeks) and with lower birth weight (1725g vs 1948g) than those with IF. Small bowel length and presence of ileocaecal valve (ICV) were not associated with IFALD. Patients evaluated for ITx had a shorter small bowel length (34.0cm vs 46.4cm) and decreased presence of ICV (38.3% vs 49.6%) compared to patients with IF.
<table>
<thead>
<tr>
<th></th>
<th>IF</th>
<th>IFALD</th>
<th>Bowel lengthening</th>
<th>Evaluated for Itx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=7371</td>
<td>n=852</td>
<td>n=681</td>
<td>n=902</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>16</td>
<td>23</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>of which liver related (%)</td>
<td>35.9</td>
<td>50</td>
<td>49.2</td>
<td>55.8</td>
</tr>
<tr>
<td>of which sepsis related (%)</td>
<td>26.8</td>
<td>34.6</td>
<td>33.1</td>
<td>25</td>
</tr>
<tr>
<td>IFALD (%)</td>
<td>46.1</td>
<td>100</td>
<td>32.4</td>
<td>54.1</td>
</tr>
<tr>
<td>Liver failure (%)</td>
<td>7.5</td>
<td>44.2</td>
<td>11.3</td>
<td>17.9</td>
</tr>
<tr>
<td>Isolated small bowel transplant (%)</td>
<td>4.73</td>
<td>3.6</td>
<td>6.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Combined small bowel-liver transplant (%)</td>
<td>4</td>
<td>15.6</td>
<td>3.5</td>
<td>12</td>
</tr>
<tr>
<td>Enteral autonomy (%)</td>
<td>57.8</td>
<td>55.6</td>
<td>54.3</td>
<td>21.1</td>
</tr>
</tbody>
</table>

[Clinical outcomes in IF patient groups]

**Conclusion:** The prognosis for patients with paediatric IF is strongly influenced and worsened by the development of IFALD. The outcome for children undergoing bowel lengthening procedures is similar to other children with IF. These data provide a clearer description of the natural history of IF which is essential for parental counselling and the design of treatment protocols.

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Family training for home parenteral nutrition of children and adolescents in the public health system in Brazil

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Objectives and Study: This study aimed to report the first training experience of the parents and relatives of children and adolescents on home parenteral nutrition (PN) from a multidisciplinary program of intestinal rehabilitation in a tertiary public hospital in Brazil.

Method: A descriptive cross-sectional study with parents and relatives of children and adolescents from the Multidisciplinary Intestinal Rehabilitation Program of a tertiary public hospital in Brazil, from July/2014 to January/2017. Inclusion criteria were: parents and relatives of children aged between 30 days and 18 years and use forecast of PN for at least 8 weeks; at least one family member who was motivated for the patient's care. Training items were: hand cleaning and washing, infusion pump handling, central venous catheter (CVC) care and PN care. The outcomes analyzed were: rate of catheter-related bloodstream infection (CRBSI); number of accidental exit of CVC; PN infusion end time with delay or advance greater than 60 minutes compared to predicted; number of mechanical obstruction of CVC; and bleeding from the site of catheter insertion and death.

Results: Twenty-seven parents or relatives of 17 children and adolescents were trained, median age was 28 (18-60) years old, of whom 62.9% were mothers. Median age of the patients was 12 (2-164) months; 14 (82.3%) were male. Eleven (64.7%) patients had short bowel syndrome and 6 (35.3%) intestinal dysmotility. Regarding the years of study, the majority (77%) of the trained family members had between 5 and 10 years of study. Forty-seven percent of the families had family income between two and three minimum wages, and 41% had less than two minimum wages. In most families (82%), the income provided basic necessities. CRBSI rate was 1.7/1000 days of catheter use and the accidental catheter exit occurred in 5 (31.2%) patients. Median age [43 (40-110) months] of patients who had accidental exit of CVC was significantly greater than those who did not have accidental exit of CVC [8.5 (4-56) months], p=0.006. Length of time on PN was significantly higher in patients who had accidental exit of CVC compared with who did not have [13 (11-30) months vs 5.5 (2-18) months, p=0.006]. There was no complication related with infusion of parenteral nutrition, bleeding or death.

Conclusion: Training the patients' family members allowed a safe execution of home parenteral nutrition with an active participation of the families. It is a feasible procedure in the public health system in Brazil.

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A survey of the use of bolus tube feeding in paediatric patients receiving home enteral tube feeding in the UK

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Objectives and Study: ESPGHAN suggest intermittent feeding wherever possible in paediatric tube fed patients as it is more physiological1. Anecdotal evidence from UK clinicians suggests bolus feeding is a common method of intermittent feeding in paediatric patients receiving home enteral tube feeding (HETF) (~16,000 paediatric HETF patients in the UK), yet there is limited information on the use of this feeding method in clinical practice. Thus a preliminary survey of current clinical practice in the UK in paediatric HETF patients was conducted to: i) estimate the number of paediatric HETF patients on bolus tube feeding regimens and; ii) characterise these patients and their regimens.

Methods: A cross-sectional survey of paediatric HETF patients receiving bolus tube feeding as all or part of their regimen was undertaken across 9 UK HETF services (Apr-Aug 2017). Dietitians estimated the number of bolus fed paediatric HETF patients from their total caseload, and for a subset of these completed a standardised questionnaire, including demographics (age, gender, medical diagnoses) and tube feeding regimen details (duration, tube type, reasons, daily feed regimen), from each patient's dietetic notes (n=155).

Results: Bolus fed patients represented 60% (n=382/635) of paediatric HETF patients, which may equate to ~9,600 total paediatric bolus tube fed patients in the UK. The survey cohort (n=155/635) had a mean age of 8y (SD 5y, range 1-16y), 57% were male and all lived at home. The patient group was diverse, with diagnoses of cerebral palsy (27%) and developmental delay (22%), and half (50%) required full assistance. Most patients were long term tube fed (mean 5y) via gastrostomy (92%) mainly due to dysphagia (62%). The decision to bolus tube feed was typically led by healthcare professionals (65%) to mimic family mealtimes (32%), top up oral diet (19%) or fit a care schedule (9%). The majority (96%) started on a bolus regimen at initiation of tube feeding, and 81% were expected to continue on a lifelong bolus regimen. Many patients were tube fed exclusively via bolus (64%) and for the remainder (36%), bolus feeding met 56% of their energy requirements. Commercial tube feeds were most commonly used to bolus (60%), with commercial oral nutritional supplements used less (13%). Most patients (70%) were fully or partially bolus fed via pump (mean volume 198ml (SD 71); duration 56min (SD 33)), with 25% via plunger (mean volume 172ml (SD 115); duration 20min (SD 18)) and 15% via gravity (mean volume 163ml (SD 75); duration 16min (SD 5)).

Conclusions: This is the first survey characterising bolus fed paediatric HETF patients in the UK, showing that bolus tube feeding is commonly used in a diverse number of paediatric HETF patients primarily to mimic mealtimes or top up oral diet, as also seen in adult HETF patients3. Paediatric patients typically received tube feed boluses via pump and less commonly via other methods, over a variety of time frames. Further exploration of the effect of different bolus tube feeding practices on paediatric patient outcomes is needed to enable recommendations for clinical practice to be made.

References:
Disclosure of interest: Emily Wong, conflict with Nutricia Ltd.; Alison Booth, Michelle Burke, Elizabeth Colyer, Hannah Ellis, Cheryl Geary, Samantha Gray, Hattie Marjoram, Alison McCarter, Lucy Stark, Amanda Wall and Elin White, none declared; Tessa Stevens, conflict with Nutricia Ltd.; Gary Paul Hubbard, conflict with Nutricia Ltd.; Rebecca Joanne Stratton, conflict with Nutricia Ltd.
Milk fat globule membrane as a source of gangliosides and phospholipids during pregnancy to support healthy pregnancy and birth outcomes

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Objectives and Study: Complex lipids, i.e. gangliosides and phospholipids, are important constituents of the central nervous system. During the final trimester of pregnancy and the first years of life, complex lipids rapidly accumulate in the developing brain; dietary supply of these lipids may optimize brain development. The milk fat globule membrane (MFGM) surrounding the milk fat globules is a dietary source of complex milk lipids (CML). Previous reports suggest that CML supplementation in pregnancy may increase levels of fetal gangliosides via placental transfer, with the potential to improve fetal brain composition and infant cognitive outcomes. We hypothesize that a higher maternal intake of CML from MFGM in pregnancy will increase complex lipid status in mother and offspring, with beneficial effects on infant brain development and general health. Our primary objective is to evaluate the impact of maternal CML intake on maternal and newborn infant CML status by comparing outcomes of CML-fortified milk with a control milk and a reference group. Our secondary objectives are to investigate the benefits of the CML-fortified maternal milk on maternal health and nutritional status, and infant general health and neurodevelopment.

Method: The CLIMB study is a randomized, multi-centre, three-group, parallel, controlled trial. We recruited 1500 pregnant women in the first trimester (11-14 weeks) living in Chongqing, China, and randomized them to one of 3 treatment groups: standard maternal milk (control), CML-fortified maternal milk (intervention), or no maternal milk with standard pregnancy advice and folic acid supplementation (reference). Control and intervention milk formulations contained DHA, probiotics, vitamins and minerals. Pregnant women followed their treatment until delivery but did not receive supplementation after birth. Maternal lifestyle and demographic data were collected throughout pregnancy, as well as biological samples (blood, hair, urine, buccal smear, cord blood, cord and placenta) and data from standard obstetric care (ultrasound reports, results of oral glucose tolerance test and pregnancy and birth outcomes). Postnatal follow-up visits were at 6 weeks and at 12 months of age, which included Bayley infant cognitive development assessment (Bayley-I).

Results: 1355 women completed the maternal intervention. Blood samples collected at enrolment and second and third trimesters were analysed for gangliosides, phospholipids, DHA, fatty acid profile, serum ferritin, plasma vitamin B12 and plasma folate. Ganglioside levels detected in the maternal blood were within expected concentrations¹ (µg/mL): GM3 (median = 7.85, IQR = 6.43-9.58); GD3 (1.55, 1.24-1.88); GT1b (0.12, 0.03-0.06), GD1a (0.10, 0.05-0.17); GD1b (0.04, 0.03-0.06). Adverse events were within expected rates for the study population, with gestational diabetes mellitus being the most prevalent adverse event and affecting 20% of women. Further pregnancy and birth outcomes will be presented.

Conclusion: The CLIMB study has already demonstrated that MFGM supplementation in the second and third trimesters of pregnancy is feasible. Determination as to whether MFGM supplementation enhances pregnancy outcomes and fetal development is ongoing.


Disclosure of interest: Gallier, S and Rowan, A are employees of Fonterra Co-operative Group Ltd, New Zealand. This work was supported by the New Zealand Primary Growth Partnership post-farm gate dairy programme, funded by Fonterra Co-operative Group Ltd and the New Zealand Ministry for Primary Industries.
Effects of mindfulness-based intervention on the treatment of disordered eating: a systematic review

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Objectives and Study: Recently, there has been increasing research interest focused on mindfulness-based interventions (MBIs) as an alternative approach for problematic eating behaviour treatment. This systematic review aims to comprehensively identify, summarize and critically evaluate current evidence from randomized controlled trials (RCTs) which use MBIs as the treatment for disordered eating concerns.

Method: Using the PRISMA method for systematic reviews, studies were systematically searched from electronic databases up to June 2017, including Ovid MEDLINE, Ovid Embase, AMED, Web of Knowledge, PsycINFO, Scopus, and the Cochrane library. Hand search of the reference lists of related systematic reviews and the first 20 pages of google scholar was conducted for detecting additional studies. Two reviewers (JY and PS) independently screened the studies. A discussion meeting was held to resolved any disagreement for final inclusion. Eligible studies are RCTs which employed MBIs as the primary intervention for people with disordered eating concern.

Results: The search produced 426 articles, of which 23 were identified for full-text review. A total of nine RCTs were finally included in this review. Main population of the included studies are adolescents. In the majority of included studies, participants in MBIs groups show significant reduction in a range of assessed outcomes, including dietary restraint, weight and shape concern, emotional eating, and external eating. Moreover, the increased mindful awareness observed in the MBIs group is significantly stronger than that in comparison arms. These findings suggest that increasing mindful awareness of internal experiences and automatic patterns related to self-acceptance, emotional regulation, and eating habits could help to reduce problematic eating behaviour.

Conclusion: This systematic review advances the understanding of MBIs as an alternative approach for problematic eating behaviour treatment. Despite the variable quality of trials and sometimes small sample sizes, the data provide initial evidence supporting the efficacy of the application of MBIs to a range of disordered eating concerns, especially in adolescents. The application of MBIs for the treatment of problematic eating merits further investigation.

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Bifidobacterium longum subsp. infantis stably restores the infant gut microbiome throughout the first year of life in breastfed infants

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Objectives of Study: Human milk has evolved to foster not only the growth of the infant, but also the shape the infant gut microbiome via complex human milk oligosaccharides. Based on historical observations of a Bifidobacterium dominant gut community in breast-fed infants, a comparative paucity of these organisms today, and the genetic adaptations specific to Bifidobacterium longum subsp. infantis, we hypothesized that supplementation of this organism to breast-fed infants would restore the gut microbiome of breastfed infantsand significantly impact the metabolome for the duration of breastfeeding.

Method: Mothers who delivered vaginally or by cesarean section received lactation support and were randomized to either provide a novel commercial preparation of Bifidobacterium longum subsp. infantis EVC001 (ATCC SD-7035) to their infants (n = 34) or not (n=32 per group). Infants consumed the preparation mixed with expressed breast milk for 21 days, and fecal samples were collected through day 60 and then through the first year of life during the introduction of complementary foods and, in some cases, the cessation of breastfeeding. Bacterial DNA was extracted from samples, and was analyzed by quantitative PCR and 16S rDNA marker gene sequencing.

Results: Invariably, infants that received EVC001 were rapidly and stably colonized at high numbers by a single strain of the organism at 10^11 CFU/g feces, while control infants had significantly lower levels of fecal Bifidobacterium. This stable colonization was evident more than 30 days after supplementation ended. Colonization by Bifidobacterium was associated with decreased relative abundances of Enterobacteriaceae, Bacteroidaceae, Clostridiaceae when compared by multivariate linear modeling. We also observed an increase in community stability during the first 60 days of life in infants fed EVC001, which accelerated community development. Bifidobacterium remained present in high levels during the introduction of complementary foods but not as infant formula replaced breast milk in the infant's diet.

Conclusion: Introduction of a novel preparation of activated Bifidobacterium rapidly and effectively resulted in a high level of Bifidobacterium longum subsp. infantis colonization in breast-fed infants, regardless of delivery mode, and remained stable through the first year of life so long as breastfeeding continued as a major portion of the infant's diet. Additionally, these dramatic changes in the gut microbiome resulted in concominant alterations to the gut metabolome, indicating potential physiological benefits to the host during the first year of life.

Disclosure of interest: Steven Frese, Giorgio Casaburi, Andra Hutton, Claire Shaw, and Ryan Mitchell are employees of Evolve Biosystems, which funded the study.

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Short term outcomes of routine vs selective fortification of human milk in preterm in a developing country: A retrospective cohort study

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Objectives and Study:
Justification: Fortification of milk has been recommended in preterms to meet the un-met nutritional needs from human milk. In a developing country, the recommendation is different considering risk of contamination, availability & associated costs of fortification. Moreover, optimising feed volume has been seen to be sufficient for short term growth parameters. Our unit policy changed from routine fortification to selective fortification in March 2017 in view of irregular availability of fortifiers, variable composition of different fortifiers & possible risk of contamination. Considering these factors, we hypothesised that selective fortification (optimizing feed volume & fortification in selected cases) in preterms growing poorly despite optimising feed volume can be considered as an alternative policy in NICU in a developing country in comparison to routine fortification (at a pre-fixed feed volume) of all preterms.

Objectives: To study the effects of routine vs selective human milk fortification on short term growth and biochemical parameters in preterm (< 32 weeks) very low birth weight (VLBW) infants.

Method:
Design: Single centre retrospective cohort study (Two different epochs - September 2016 to February 2017 as “Routine fortification” epoch & March 2017 to August 2017 as “Selective fortification” epoch)
Setting: Department of Pediatrics & Neonatology at a tertiary care centre in India
Participants: Preterm infants weighing ≤ 1500 grams and ≤ 32 weeks of gestation included. Infants with major congenital abnormalities excluded.
Main outcome measures:
Primary: Rate of growth till discharge.
Secondary: i) Biochemical parameters (Worst calcium, phosphate and Hb) ii) Adverse outcomes (feed intolerance, NEC, sepsis)

Results: During the study period, 52 infants were eligible out of which 1 infant with major malformation was excluded. Mean gestational age (Routine - 29.5 Vs Selective - 29.9 weeks, p=0.5) & median birthweight (Routine - 1230 vs Selective - 1202 g, p = 0.4) were comparable. The median rate of weight gain (g/kg/d) in the routine fortification group [10.8 (3.3, 17.1)] was comparable to that in the selective fortification group [8.4 (0, 14.2), p = 0.6] (Table I). Serum PO4 showed a significantly higher value in the selective fortification group (5.9 vs 4.8, p=0.03) with rest of the metabolic parameters showing a trend towards a favorable outcome in the selective fortification group. Adverse outcomes too showed a trend towards decreased feed intolerance, NEC, sepsis in the selective fortification group, although statistically not significant. The median duration of hospital stay (days) between the two epochs were also comparable [17 (6.2, 36.2) in the Routine group Vs 17 (6, 28) in the Selective group, p = 0.9].

Conclusion: Selective fortification had a comparable growth rate & showed a trend towards better metabolic parameters than routine fortification of human milk. Also, selective fortification appears less harmful and a trend towards lesser adverse outcomes compared to routine fortification. So, a larger properly designed study needs to be carried out in a developing country to define the indication of fortification in preterms as well as long term outcomes of fortification.
<table>
<thead>
<tr>
<th>Variable</th>
<th>“Routine Fortification” Cohort (n=28)</th>
<th>Selective Fortification” Cohort (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMF usage, n (%)</td>
<td>14 (50%)</td>
<td>5 (21%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Rate of weight gain (g/kg/d), median (1st, 3rd quartile)</td>
<td>10.8 (3.3, 17.1)</td>
<td>8.4 (0, 14.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Day of regaining birth weight, median (1st, 3rd quartile)</td>
<td>12.5 (9, 16.7)</td>
<td>13 (6, 16)</td>
<td>0.6</td>
</tr>
<tr>
<td>Lowest Ca (mg/dL), mean (SD)</td>
<td>10.2 (1)</td>
<td>10.1 (1.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Lowest Po4 (mg/dL), mean (SD)</td>
<td>4.8 (0.98)</td>
<td>5.9 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lowest Hb (gm/dL), mean (SD)</td>
<td>10.7 (2.8)</td>
<td>12 (3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Feed intolerance, n (%)</td>
<td>10 (37%)</td>
<td>8 (40%)</td>
<td>1</td>
</tr>
<tr>
<td>NEC, n (%)</td>
<td>3 (11%)</td>
<td>1 (5%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>16 (59%)</td>
<td>11 (52%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

[Table I: Comparison between two cohorts]

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Early postnatal growth failure in preterm infants is not inevitable

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Objectives and Study: Initial weight loss with an accompanying drop across centile lines in infants born preterm is well described in the literature, with some authors concluding that this is an inevitable consequence of preterm birth. This pattern persists during the first weeks of life and infants reach term equivalent age significantly lighter and with smaller head circumference than their term equivalent counterparts. This suboptimal early growth pattern is likely to impact on short, medium and long-term health outcomes. We describe a single neonatal unit's experience of longitudinal preterm weight gain in a recent cohort of preterm babies born at less than 32 weeks' gestation, where providing optimum nutrition was a focus of care, using routinely captured electronic growth data.

Methods: Data were collected from a single neonatal unit between July 2012 and October 2017 and recorded electronically. Infants born less than 32 weeks were included. Infants were weighed at least weekly. Patients were grouped according to their gestational age at birth (in weeks) and growth was plotted according to their corrected gestational age. Growth curves representing the 50th centile were constructed for each cohort using the LMS method and overlaid on the current UK growth standard marked centile lines. All groups' data were examined for initial absolute weight loss. Standard deviation scores (SDS) were calculated in the subgroups at birth and 36 weeks' gestation. Change in SDS from birth to 36 weeks was calculated using data only from infants who were present from the first week of life up to 36 weeks corrected gestational age.

Results: 396 babies with 2808 weights were analysed. 50th centile longitudinal growth curves were generated by gestational age at birth. This data did not demonstrate an initial absolute weight loss in any of the subgroups analysed (figure 1). Across all groups the mean fall in standard deviations score between birth and 36 weeks was -0.27 of a SDS, meaning they did not drop more than a marked centile line. There is an initial relative downward trend compared to the centile curves, but a drop down across marked centiles was not seen, except for the 23 week subgroup who fell by a SDS of and -1.02 respectively for weight between birth and 36 weeks.
Conclusion: This description of longitudinal weight gain in a cohort of preterm infants demonstrates that early postnatal growth failure is not inevitable, with most infants following close to their birth centile until discharge. The growth curves depicted differ significantly from previously published longitudinal weight gain data. We do not see here the previously reported 2 marked centile lines decrease or early weight loss in any the subgroups. These data provide evidence to suggest that extrauterine weight gain tracking centile lines can be achieved in preterm infants. This has the potential to ameliorate the growth deficit they exhibit at term equivalent age, the subsequent need for catch up growth and increased risk of non-communicable diseases in later life.

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Perinatal Stress Induced Hyperinsulinemic (PSHI) hypoglycemia in neonates admitted in NICU: A case series

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Objective and Study: Hyperinsulinemic hypoglycemia (HIH) is generally considered as a genetically heterogeneous disorder with both familial and sporadic variants. However, infants presenting during the neonatal period, may show transitional, transient or persistent hyperinsulinemic features and many a times this could happen due to perinatal stress induced hyperinsulinism (PSHI). In this study, we aimed to discuss our experience with HIH patients, based on a series of 111 patients presented with hypoglycemia.

Methods: We retrospectively analysed the clinical and laboratory characteristics of neonates admitted with hypoglycaemia during the period between January 2013 to December 2016.

Results: During this period 111 patients admitted with hypoglycemia & out of this only 23 (21%) infants were symptomatic. Total 14 (12.6%) infants had hyperinsulinemic state during the course of evaluation. All infants (8 males, 6 females) presented during the first 48 hours of life. Mean GA & birth weight was 35.5 weeks and 2400 grams respectively. Commonest risk factors among PSHI were Cesarean section (71%), SGA (50%), fetal distress (28.5%). Only one of the mother had gestational diabetes. None of the baby had any seizure or encephalopathy during hospitalization. 9 (64%) out of 14 infants required diazoxide & 3 (21%) infants also required octreotide during hospitalization. However, none of the infant failed to medical treatment.

Conclusions: Strong clinical suspicion is needed in cases of hypoglycemia requiring high GIR because Perinatal Stress Induced Hyperinsulinism (PSHI) is the commonest factor & most would recover with medical management in few days to weeks.

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Prematurity and early adiposity rebound: a cohort study

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Objectives and Study: The adiposity rebound (AR) corresponds to the second rise in BMI curve that occurs physiologically between ages 5 and 7 years. The timing of the adiposity rebound has a great effect on children’s health, being associated with the development of metabolic disease for life. Objective of this study was to assess the rate of early adiposity rebound in a cohort of premature infants.

Method: To assess the rate of early adiposity rebound in a cohort of premature infants, growth data were monitored longitudinally. Weight, length, and BMI were measured at birth and at 1, 3, 6, 9, 12, 15, 18, 24 months and 3, 4, 5, 6, 7 years of gestation-corrected age. Timing of AR was assessed by visual inspection of body mass index plots.

Results: Of the 411 preterm newborns eligible, only 59 completed the 7 years follow-up and entered in the final analysis. AR occurred significantly earlier in 52.5% of the premature infants enrolled. The early AR had occurred in 50% of the patients born late preterm (34-36 weeks’ gestational age) and in 58.11% of the patients born moderate and extreme preterm (<34w) (chisquare= 0.12 p=0.728). An early AR is associated with an higher BMI at 6 years of gestation-corrected age (BMI means :17.3 vs 14.64; t=4; p<0.0001).

Conclusion: Clinical management of infants born preterm should focus on minimizing excess weight gain to reduce long-term metabolic risk. Moderate and extreme preterm infants not seemed to be at higher risk for early adiposity rebound respect late preterm.

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Maternal postnatal psychosocial distress and its association with cortisol levels and immunological composition in breast milk

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Objectives and Study: The beneficial influences of breastfeeding on infant health are widely recognized. A wealth of bioactive factors in breast milk (BM) seems responsible for these effects, including oligosaccharides, bacteria and immune components. Some studies indicate that maternal mood is related to alterations in immunological components of human milk. However, studies investigating the relationship between maternal postnatal psychosocial distress using in-depth profiling techniques assessing a broad panel of immune factors are scarce. Furthermore, limited information is available on the levels of increase/decline of immune components and cortisol during the first months postpartum in relation to maternal mood. This study investigated the association between maternal postnatal psychosocial distress (e.g. anxiety, depression and stress), cortisol and immunological components in BM, including immunity factors (IL1β, IL6, IL12, IFNγ, TNFα, IL2, IL4, IL10, IL13, IL17), chemokines (L8, Groα, MCP1, MIP1β), growth factors (IL5, IL7, G-CSF, GMCSF, TGFβ2) and immunoglobulins (IgA, total IgG, IgM) across the first three months postpartum.

Method: Milk samples from 59 healthy mothers after full term pregnancies were collected at three time points during the first three months post-delivery. Maternal postnatal psychosocial distress was measured using self-reported questionnaires simultaneously. BM immune compounds were quantified by magnetic beads-based multiplex immunoassays. Cortisol levels were quantified by liquid chromatography-tandem mass spectrometry. Multivariate analyses were performed to assess the association between maternal postnatal psychosocial distress and milk immune and cortisol levels.

Results: All the assayed immunological factors were detected in all milk samples over the first three months postpartum, with the exception of GMCSF. The concentration of immunological factors significantly decreased during the first three months postpartum for IgG (p<0.001), IgM (p<0.001), IL6 (p=0.002), MCP1 (p<0.001), MIP1β (p<0.001), GROα (p=0.003), EGF (p=0.015), and TGFβ2 (p=0.003). Cortisol was detected in almost all samples and its concentration significantly increased over time (p=0.031). Significant differences were observed in milk immune factors and cortisol between mothers with high psychosocial distress compared to mothers with low psychosocial distress. Mothers with low psychosocial distress had lower cortisol concentrations in their BM compared to mothers with high psychosocial distress, reaching significance at week two postpartum (p=0.029). Additionally, mothers with low psychosocial distress compared to women with high psychosocial distress had significant higher concentrations of IL5 and G-CSF two weeks postpartum and significant lower numbers of IL5 and IgM at 12 weeks post partum.

Conclusion: Breast milk of mothers is characterized by changes in abundance of immunoprotective, pro-inflammatory compounds and cortisol during the first three months postpartum. The kinetics of increase/decline were different between mothers with high and low self-reported psychosocial distress for cortisol, IL5, G-CSF and IgM. The relevance of these changes for infant health requires future research.

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Do all trans-C18:1 intakes during pregnancy jeopardise polyunsaturated fatty acid status in new-borns? Focus on a trans-vaccenic acid (trans-C18:1 n-7) supplementation in the rat

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Objectives and Study: Trans-octadecenoic acids (trans-C18:1) intakes during pregnancy were previously shown to threaten polyunsaturated fatty acid (PUFAs) status in new-borns. However, a distinction should be made between trans-C18:1 positional isomers regarding their impact on human health. If industrial trans fatty acids are known to be harmful, less is known about dairy trans fatty acids such as trans-vaccenic acid (trans-C18:1 n-7, TVA). Studying one isomer at a time remains indeed a technical issue in terms of both purity and elevated amount. Overcoming such a challenge, this study aimed at focusing only on TVA, studying the impact of its supplementation during pregnancy on PUFAs status in new-borns.

Method: We first chemically synthesised cis-vaccenic acid (cis-C18:1 n-7, CVA), then isomerised it to yield TVA. Liquid Chromatography Flash, an innovative means, enabled the separation between TVA and CVA, according to a 95%-purity. Second, pregnant Sprague-Dawley (day 14) were used and fed with either a TVA-supplemented diet (2% of total energy), or a CVA-supplemented diet (2% of total energy, control) for three weeks. The linoleic acid/α-linolenic acid ratio was settled at 5 in both diets. Regarding pups, their diet relied exclusively on maternal milk for two weeks. Fatty acid composition of plasma, red blood cells, muscle, adipose tissue, liver and brain of pups was assessed by GC-MS. Data analysis relied on both univariate statistics and a recently developed multi-block procedure that modelled lipid metabolism and interaction between tissues.

Results: First, chemical synthesis of TVA was successful, yielding high amounts of pure TVA almost without any other trans-C18:1 isomer. Second, TVA was incorporated in all tissues analysed in the pups fed the TVA diet, including the brain (0.19% of total fatty acids). Compared to control, univariate analyses only revealed a significant decrease in C22:4 n-6 in the brain of pups fed the TVA diet; otherwise, non-significant decreases in arachidonic acid and DHA were found in these pups. In key tissues such as plasma and red blood cells, non-significant increases in both n-6 and n-3 PUFAs in the TVA group were highlighted. The multi-block procedure unravelled a discrimination between both groups, but consistently with univariate outcomes, PUFAs played a weak role in this separation.

Conclusion: This study focused on one accurate trans-C18:1 isomer, namely TVA. Its supplementation during pregnancy may not jeopardise PUFAs status in new-borns, but other studies are needed to both draw accurate conclusions and understand the physiological impacts of TVA. As the current consumption of partially hydrogenated oil decreases in developed countries, dairy trans fatty acids will account for a larger part of trans fatty intakes in the forthcoming period. Their impact on human health in general should be properly assessed. Our study underline that solutions do exist to obtain one very pure isomer in high amounts. Our outcomes call for more studies about the relationship between dairy trans fatty acids intakes during pregnancy and PUFAs' status of new-borns.

Disclosure of interest: Etienne Guillocheau is part of the French Dairy Interbranch Organization (CNIEL).

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Maternal postnatal psychosocial distress: associations with the breast milk microbiome

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Objectives and Study: Breast milk (BM) is the most important source of nutrition for millions of infants worldwide. It transfers many bioactive components to the developing infant, including a diverse community of microbes. The bacterial strains in BM vary greatly between women and are subject to changes over time. It remains largely unknown which maternal factors may explain the variation of microbial development in BM during the first months postpartum. One maternal factor that may impact BM microbial composition is maternal postnatal psychosocial distress. This study investigates the association between maternal postnatal psychosocial distress (i.e. anxiety, stress and depression) and BM microbiota composition across the first three months postpartum.

Method: This study was carried out on a healthy population of 59 mothers after full term pregnancies. Maternal postnatal psychosocial distress were measured using self-reported questionnaires during the first 3 months post-delivery. Milk samples were collected simultaneously. For BM microbial identification, Illumina technology based on sequencing of the 16S ribosomal RNA gene was used.

Results: Overall, at the phylum level, Firmicutes were the most frequent and abundant bacterial phyla (albeit decreasing over time), followed by Proteobacteria and Actinobacteria (both increasing over time). Within the phylum Firmicutes, Staphylococcaceae and Staphylococcus, respectively Family and Genus, were the most abundantly and frequently present, and both decreased over the 3 month period postpartum. Family Streptococcaceae and Genus Streptococcus were the second most abundant and frequent phyla present and their levels remained stable over time. Levels of maternal postnatal anxiety, stress and depression were independently associated with changes in the composition of milk microbiota at the different time points. Low levels of maternal postnatal anxiety were associated with lower reads two weeks postpartum of Family Enterococcaceae and Genus Enterococcus compared to higher levels of maternal postnatal anxiety. Moreover, low levels of maternal postnatal anxiety were associated with a higher number of reads two weeks postpartum of the Family Actinobacteria and the species Bilidobacterium infantis. The amount of reads belonging to the Order Lactobacillales were higher in milk from mothers with low levels of anxiety compared to milk samples from mothers with high levels of anxiety. Regarding maternal postnatal stress, the number of reads two weeks postpartum corresponding to Class clostridia, Family Veillonellaceae, Family Streptococcaceae and Genus Veillonella were highest in milk samples of mothers with low/medium levels of stress. For maternal postnatal depression, sequences related to Genus Fusobacterium were only detected in milk samples from mothers with high levels of depression.

Conclusion: This study shows an association between maternal postnatal psychosocial distress and microbial composition in healthy breastfeeding women up to three months postpartum. Class bacilli, Order Bacillales, Genus Staphylococcus and Class Actinobacteria mainly drove the differences between both groups. Existing evidence warrants further exploration of the BM microbial ecology.

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Effects of processing of bovine colostrum on levels of bioactive proteins

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Objectives and Study: Fresh bovine colostrum (BC) contains high levels of bioactive proteins, such as immunoglobulins (IG), lactoferrin (LF) and lactoperoxidase (LP). In preterm pigs, BC induces intestinal maturation, improves growth and protects against necrotising enterocolitis (NEC). Based on this, clinical trials using spray-dried, pasteurized BC to improve gut maturation in human preterm, have been initiated. It remains to be tested how different industrial processing may preserve the stability of colostrum proteins and help to secure high bioactivity of colostrum products used for infants.

Method: Untreated BC (control) from Danish dairy cows (Biofiber Damino, Denmark) was subjected to low-temperature long time pasteurization (LTLT, 62.5°C, 30 min) or high-temperature short time pasteurization (HTST, 72°C, 15 s). All products were then spray-dried (SD), with or without a final step of γ-irradiation (GI, ~14 kGy) to remove possible contamination during packaging. Samples were analysed for protein content and by nitrogen solubility index to determine protein denaturation (pH 4.6, removal of aggregated proteins and analysis of protein in the filtrate). IG and LF were determined by ELISA and Western blotting (WB). Proteins were separated by SDS-PAGE and compared with protein standards for identification and semi-quantified by densitometry, relative to values in a non-treated liquid BC sample. Proteomic analysis using LC-MS/MS of trypsin-treated samples was used to identify and quantitate the abundance of modifications.

Results: SD increased denaturation by 6% relative to non heat-treated BC. GI increased protein denaturation to 11%. LTLT increased denaturation to 19% which rose to 27% following GI. HTST increased denaturation to 48% with no further increment following GI (all P < 0.05).

LTLT resulted in 15% denaturation of total IgG compared to non-pasteurized BC, but not significantly. GI raised denaturation to 29%. HTST denatured total IgG by 34%, rising to 58% following GI (all P < 0.05, except for LTST alone (NS)). Compared to untreated BC, SD of unpasteurized BC had no effect on IgG1 levels, however GI increased denaturation of IgG1 (30%, P < 0.05). LTST caused no loss of IgG1 but GI increased denaturation, (38%, P < 0.05). HTST also increased denaturation to 40% but GI changed this to 60%. Levels of IgG2 mirrored those of IgG1, however it was more labile than IgG1 under LTST and HTST (P < 0.05). LTST led to a 21% reduction in LF and GI further reduced this (47%, P < 0.05). LTLT, and HTST, reduced the levels of LP (56 and 81% respectively) which were further reduced by GI. WB indicated aggregation of LF with HTST. Compared to unheated BC, differences in total methionine oxidation were observed, which were significant in the LTST plus GI treated BC (P < 0.05). No significant differences in total methionine oxidation were observed between untreated BC and LTST and HTST-treated BC.

Conclusion: BC proteins are highly sensitive to processing and the greatest effects are observed with HTST pasteurization. Further, high-dose GI treatment affects the stability of bioactive proteins, especially when combined with HTST processing. In conclusion, LTST followed by SD is an optimal way to preserve the levels of important colostrum bioactive proteins.

Disclosure of Interest: Tim Hesselballe Hansen is an employee of Biofiber-Damino A/S All other authors have no conflict of interest.

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The study of human β-defensins concentrations in Chinese human milk and immunoregulation function of neonate umbilical cord blood T, B and dendritic cells

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Objectives and Study: Human β-defensins (HBD) in human milk play an important role in human innate and adaptive immune system. However, research about β-defensins in the breast milk of Chinese women remain is limited. What’s more, the effect of immunoregulation of HBDs is an area little research has been done. In the present study, we examined the concentrations of HBD-1 and HBD-2 in the human milk of healthy Chinese. Moreover, we evaluated immunoregulation of HBD1 on neonate umbilical cord blood (CB).

Method: 100 mother-infant pairs were recruited in this study. Breast milk concentration of HBD-1 and HBD-2 in colostrum and mature milk were tested by ELISA kits. Measurement of HBD-1 and HBD-2 mRNA was done by quantitative real-time PCR. The proliferation of cord blood CD4+ T lymphocytes which was treated with HBD1, PHA or co-treated with both was detected by CCK-8. The expressions of CD80, CD86 on B cells and CD69, CD25, CD40L, CD45RO, IL-2 on CD4+T cells were detected by FACS. Purified monocytes were cultured with GM-CSF and IL-4 in the presence or absence of HBD1. Then, the differentiated imDCs were further stimulated with LPS in the presence or absence of HBD1. The expressions of CD14, CD1a, MMR, CD11c, CD40, CD86 and MHCII on DC were detected by FACS. Endocytosis of DC was measured by uptaking FITC-dextran and Latex beads. Monocyte-derived DC were treated with mitomycin C and cultured with CFSE labeled CD4+ lymphocytes, and the proliferation of CD4+T was detected by FACS. The secretion of IL-6, IL-10, TNF-α and IL12p70 were measured by ELISA. The apoptosis was determined by Annexin V/PI kit.

Results: The concentration ranges of HBD-1 and HBD-2 in the colostrum were found to be 1.04-12.81 mg/ml and 0.31-19.12 ng/ml, respectively. In mature milk, the concentration ranges were 1.03-31.76 ng/ml for HBD-1 and 52.65-182.29 pg/ml for HBD-2. HBD-1 concentration and mRNA expression were significantly higher than that in HBD-2 both in the colostrum (P<0.001) and in mature milk (P<0.001). The proliferation of cord blood CD4+T lymphocytes can be stimulated by HBD1. The expression of CD80, CD86 on CB B cells and CD69, CD25, CD40L on CB CD4+T cells can be up-regulated by HBD1. The expression of CD80, CD86 on CB B cells and CD69, CD25, CD40L on CB CD4+T cells can be up-regulated by HBD1. What else, the secretion of IL-2 from cord blood CD4+T cells can be promoted by HBD1. HBD1 facilitated the differentiation and decreased endocytic activity of human CB monocytes-derived immature DC, promoted the maturation of human CB monocytes-derived immature DC, and inhibited the apoptosis of immature and mature DC. HBD1 treated immature and mature DC promoted allogeneic lymphocyte proliferation. In addition, HBD1 also promoted the proliferation and activation of human CB T cells.

Conclusion: In breast milk from healthy mothers, concentrations of HBD-1 and HBD-2 were high, and HBD-1 was a little higher than HBD-2. The concentrations of both HBD-1 and HBD-2 in early lactation in human milk were higher than those in late lactation. HBD1 can regulate the immunological function of neonate umbilical cord blood by activating CD4+T cells, promoting the differentiation and maturation of immature DC, and boosting the proliferation and activation of human CB T cells co-incubated with DC, all of which may have an essential role on infants’ immune function development.

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The variations of stool patterns in a large group of healthy infants from birth to the 24 months of age

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Objectives and Study: The stool patterns in the first two years of life may be considerable various, in which cause the concerns of parents. The objective of this study was to identify the normal stool patterns and the factors affecting these patterns in a large group of healthy infants.

Methods: This cross-sectional survey using an on-line questionnaire was conducted to the parents who volunteered to participate in Maeil Infant Stool Analysis Research (MISAR) from November 2009 to August 2016. The questionnaire composed of 21 items of the feeding type, stool patterns and symptoms related with feeding type.

Results: A total of 19,505 healthy infants from birth to 24 months of age were enrolled in this study. There were no significant differences in gender, delivery type, and birth weight between breast-fed (n=5,109), formula-fed (n=8,772), and mixed-fed (n=5,624) infants. The stool frequencies were significantly higher in breast-fed infants (mean ± SD: 12.4±10.4) than in formula-fed (10.4±6.3) and mixed-fed (10.9±9.7) infants (P<0.05). The frequency of vomiting during or after feeding were significantly lower in breast-fed infants (2.3±1.7) than in formula-fed (2.5±2.1) and mixed-fed (2.4±2.0) infants (P<0.05). Breast-fed infants showed significantly softer stool (Bristol stool scale of 6 or 7) and more yellow (lesser green) colored stool than formula-fed and mixed-fed infants during the 6 months of age (P&LT; 0.05). However, after the 6 months of age, no significant differences of stool consistency and color were observed between three groups (P>0.05). Significant predictors of stool softness were found to be age (&LT; 1mo: odds ratio [OR]=1; 1-3mo: OR=1.86, 95% CI=1.59 to 2.18; 4-6mo: OR=1.8, 95% CI=1.54 to 2.09; 7-12mo: OR=0.17, 95% CI=0.15 to 0.2; 13-23mo: OR=0.04, 95% CI=0.03-0.05) and feeding type (breast feeding: OR=1; formula feeding: OR=0.58, 95% CI=0.54 to 0.64; mixed feeding: OR=0.85, 95% CI=0.77 to 0.95), after adjusting the relevant factors. Significant predictors of yellow or green colored stool were found to be age (&LT; 1mo: OR=1; 1-3mo: OR=0.53, 95% CI=0.28 to 1.01; 4-6mo: OR=0.41, 95% CI=0.22 to 0.78; 7-12mo: OR=0.26, 95% CI=0.14 to 0.49; 13-23mo: OR=1.05, 95% CI=0.44-2.52) and feeding type (breast feeding: OR=1; formula feeding: OR 0.54, 95% CI=0.40 to 0.73; mixed feeding: OR=0.49, 95% CI=0.36 to 0.67), after adjusting the relevant factors.

Conclusion: In the first 6 months of life, breastfed infants have more frequent, softer and more yellow colored stools than formula-fed and mixed-fed infants. This is the first study to investigate the stool patterns of a large group of healthy infants in South Korea. These findings can guide parents, and clinicians in distinguishing normal from abnormal stool pattern to avoid the unnecessary medical treatment.
Shorter episodes of crying in infants receiving a formula with a prebiotic blend

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Objectives and Study: Few studies have evaluated the nutritive effects of prebiotics early behavioral indicators of tolerance. The daily duration of crying and fussing in infants typically increases from birth, peaks around 6-8 weeks of age, and subsequently decreases with age. Cortisol is connected to stress response and has been evaluated using salivary cortisol in infants. The cortisol awakening response (CAR) emerges ~2 to 6 months of age. Consequently, the objective of this study was to assess infant state and CAR in infants randomized to receive: cow's milk-based infant formula without added prebiotics (Control, n=82) or with prebiotic ingredients (polydextrose [PDX] and galactooligosaccharides [GOS]; 4 g/L, 1:1 ratio) (PDX/GOS, n=79) from baseline (14-35 days of age) up to 112 days of age.

Method: In this multi-center, double-blind, controlled, parallel-group, prospective pilot study, parents/caregivers used a validated parent-report diary to record crying/fussing and awake/content behavior at three study time points (consecutive 72 h periods at baseline, Day 70, and Day 112) in healthy term infants. Duration (min) of crying/fussing and awake/content was analyzed by mixed-effects models.Participant saliva samples were collected at home within 48 h prior to Day 70 and 112 study visits 1) directly upon first wakening and 2) 30 minutes post wakening. Salivary cortisol (µg/dL) was immunoassayed and analyzed by mixed-effects models.

Results: Significant age-related changes were demonstrated by study end with a decrease in crying frequency (number of episodes) and total duration of crying (P≤0.033). Baseline crying frequency and duration of crying per episode (mean ±SE) (Figure) were not different between groups. Although no group differences in crying frequency were detected at Days 70 and 112, duration of crying per episode was significantly lower for the PDX/GOS compared to Control at Day 70 (P=0.017) and continued the same trajectory at Day 112 (P=0.089). Moreover, a trend in reduced duration of nighttime crying per episode at Day 70 was observed. The presence of CAR was demonstrated at Days 70 and 112 in both groups.

Conclusion: Shorter episodes of crying were demonstrated by Day 70 in infants receiving formula with prebiotics - a time point corresponding to the same age and developmental range typically associated with peak crying. Results suggest improved behavioral indicators of tolerance in infants receiving a prebiotic blend and provide further support the need to assess the connection of nutrition and infant state throughout the first months of life. The effect of prebiotics on infant state is consistent with an influence on the gut-brain axis and requires further study.
Disclosure of interest: This research was funded by Mead Johnson Nutrition. The presenting author is an occasional consultant for Mead Johnson Nutrition.

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Enteral nutrition tolerance in very low birth weight infants with mild respiratory distress syndrome treated with high flow nasal cannula therapy

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Objectives and Study: The aim of our study was to evaluate the time to reach full enteral feeding (defined as a daily intake of ≥ 140 mL/kg/day) in very low birth weight infants with mild respiratory distress syndrome (RDS) treated with High Flow Nasal Cannula Therapy (HFNCT). Secondary outcomes were percentage of patients that did not need mechanical ventilation, rate of bronchopulmonary dysplasia (BPD), air leaks, nasal injury, late onset sepsis (LOS), intraventricular hemorrhage (IVH), retinopathy (ROP), necrotizing enterocolitis (NEC), hemodynamically-significant patent ductus arteriosus (PDA) and death. Mean duration of total parenteral nutrition, mean time to full suckling feeds and duration of hospitalization were also evaluated.

Method: We retrospectively studied medical record from January 2014 to December 2016 of very low birth weight infants with mild respiratory distress syndrome (RDS) treated with HFNCT.

Results: 64 VLBW preterm newborns were enrolled. Mean time to reach full enteral feeding was 14.6±9.4 days. The overall success rate, i.e. no mechanical ventilation within 72 hours after nHFT, was 93.7%. BPD was diagnosed in 26.6% of preterms enrolled. Neither air leaks nor nasal injury were recorded as well as no exitus occurred. LOS, IVH, ROP, NEC and hemodynamically-significant PDA occurred respectively in 16.1%, 0%, 7.8%, and 1.6% of newborns. Mean duration of total parenteral nutrition was 13.0±9.3 days. Mean time to full suckling feeds was 32.1±15.0 days. Duration of hospitalization was 52±20 days.

Conclusion: We can speculate that HFNCT had indirect benefit on Enteral Nutrition Tolerance in Very Low Birth Weight Infants with Mild Respiratory Distress Syndrome, due to a simple interface and small tapered prongs perceived as more comfortable for the newborns.

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Breast feeding versus formula feeding of neonatal thrombocytopenia infants of mothers with chronic immune thrombocytopenia

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Introduction and aim of study: Immune thrombocytopenia (ITP) in pregnant women can cause neonatal thrombocytopenia by transport of antiplatelet autoantibodies across the placenta. Usually, an infant's platelet count normalizes within 2 months. In this study we evaluate of platelet counts in infants with breast feeding versus of formula type in mothers with chronic immune thrombocytopenia either with presence or absent of maternal antiplatelet antibodies.

Subjects: Thirty neonate with thrombocytopenia with history of maternal chronic immune thrombocytopenia (platelet count less than 100000/µL were included to this study at Pediatric Hematology and Oncology Unit of Zagazig University In Egypt, during period from 2000 to 2017. Those Neonate were Classified into four groups according to:

1-Feeding type Group 1: Brest fed neonate 17 and Group 2 Formula fed infants with formula fed 13 neonate. According to maternal antiplatelet antibody into group A negative for antiplatelet antibodies included 21 cases. And Group B that with positive antiplatelet antibodies included 9 cases.

Methods: All patients were full history of maternal chronic immune thrombocytopenia as well full details of neonatal history included bleeding and feeding. Complete blood picture was done regularly for 8 weeks.

Results: The initial mean platelet number had no significant difference between neonate groups with thrombocytopenia. There was no significant differences of increase platelet count among different groups. The period recovery in days had no significant difference.

Conclusion: Breast feeding is not harmful of neonatal thrombocytopenia of mothers with chronic immune thrombocytopenia either with positive or negative antibodies and further researches are recommended

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Analysis of nutritional support in VLBWI with extra-uterine growth restriction

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Objectives and Study: To assess the incidence of extra-uterine growth restriction (EUGR) in very low birth weight infants (VLBWI) and evaluate the nutritional problems in VLBWI associated with inadequate nutrient intakes during hospitalization.

Method: VLBWI (1,000-1,499 g) were admitted to the NICU of Xin Hua Hospital from October 1, 2012 to October 1, 2016. One hundred and twenty eight VLBWI were divided into a EUGR group (n = 87) and a non-EUGR group (n = 41). Growth and parenteral (PN) and enteral (EN) nutrition practices were analysed. Actual energy and protein intakes were subtracted from recommended energy (120 kcal/kg/d) and protein (3.75 g/kg/d) intakes and nutritional deficits were calculated.

Results: Growth restriction was 21.9% at birth and 68.00% at discharge. Compared with established guidelines, PN was started late, and the maximum amino acid supply was low in both groups. EN interruption rate was higher in the EUGR group. The average energy intake in the 1st day after PN termination was lower in the EUGR group. Further analysis of actual intakes, the differences of the sum percentages of parenteral and enteral energy and protein accounted for recommendations in two groups were only in several weeks during hospitalization, so did daily energy and protein intakes. However, the cumulative energy and protein deficits were significantly higher in the first eight weeks and during the 3rd to 7th weeks in the EUGR group. Body weight z-scores decreased with increasing cumulative energy and protein deficits.

Conclusion: Inadequate nutrition intake aggravated the occurrence of EUGR in VLBWI.
Changes of cumulative energy and protein deficit and weight z scores in two groups in VLBWI

[Figure 1]

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NUTRITION - Neonatal and infant nutrition

N-P-101

Cumulative energy intakes in the first two weeks of life are associated with hospital outcomes in birth weight less than 1500 g infants

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Objectives and Study: To evaluate cumulative energy intake in the first two weeks of life in birth weight less than 1500 g infants and to determine the relationship between energy intake and outcomes these infants.

Method: It was a prospective, nonrandomized, observational study in very low birth weight infants (birth weight ≤1500 g). Energy intake and hospital outcomes were assessed in 42 premature infants (average birth weight: 1204±202 g, 665~1480 g) who were hospitalized within 24 hours after birth in neonatal intensive care unit. Infants received parenteral nutrition (PN) and enteral feeding (EN) according to clinical status. Infants were separated into those who received a cumulative energy intake less than the average calorie (73 kcal/kg/d) and those who received an intake over the average (≥ 73 kcal/kg/d) during the first two weeks of life.

Results: Lower cumulative energy intake in the first two weeks after birth was associated with a significantly increased duration of PN (28.3±9.8 days vs 22.9±7.2 days, p=0.045), a later EN beginning (5.9±3.6 days vs 3.6±2.0 days, p=0.011) and a lower growth velocity of the first two weeks after birth (4.7±4.9 g/d vs 14.5±9.0 g/d, p=0.0001). It also associated with a significant increase in the length of hospitalization (54.8±15.4 days vs 43.0±10.8 days, p=0.006), longer time of artificial ventilation (22.8±14.0 days vs 16.1±12.4 days, p=0.0011) and more hospitalization costs (¥1464±494 per day vs ¥1251±464 per day, p=0.0008). In 42 infants, cumulative energy intake in the first two weeks of life was positively related to total cumulative energy intake in the hospital (r=0.350, p=0.023), time to EN beginning (r=0.482, p=0.001), length of hospitalization (r=0.376, p=0.014) and total hospitalization costs (r=0.377, p=0.014).

Conclusion: The early energy intake is an important determinant of outcomes. Cumulative energy intake in the early period of life may be drastically improved the hospital outcomes in these birth weight less than 1500 g infants.

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Nutrition in infants undergoing surgery for congenital heart disease. A longitudinal study in 71 children

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Objectives and Study: Congenital heart diseases (CHDs) represent a current global health problem because of rising long-term survival over the last 20 years. Poor growth that is a common consequence of CHDs with underfeeding being the most frequent cause of growth failure. Poor growth status is associated with increased perioperative and long-term complications. Previous studies on children with CHDs requiring surgery have indicated the most vulnerable period for growth impairment in this category of patients being the first 6 months of life.

Method: Our retrospective study assessed weight trend and nutrition practices in 71 infants undergoing surgery for CHDs within the first 6 months of life to identify nutritional care critical periods that could be improved. We included all the infants admitted to the Department of Paediatric and Congenital Cardiac Surgery between 1/1/14-31/12/14 who required surgery.

Results: Prevalence of underweight (weight for age z score, WAZ< -2) was already 8.6% at birth and remained unchanged until 1 year after surgery (T5). The median WAZ decrease was -0.78 from time of surgery (T1) to discharge (T3). T3 WAZ was significantly associated with T1 WAZ and postoperative period (T2) WAZ while T5 WAZ was significantly associated with T3 WAZ: pre-operative underweight persisted for a long time after surgery. T1 WAZ was significantly associated with intracardiac shunt and incompatible postnatal circulation CHDs. Length of stay (PODs) was significantly associated with T1 WAZ regardless of CHD physiopathology. As concern nutritional data, enteral feeding was initiated at a median time of 3 days, while full oral feeding was achieved at a median time of 7 days. The evaluation of ingested calories showed a statistically significant difference between prescribed and delivered enteral calories at T1 (p=0.0339) and T2 (p=0.0008).

Conclusion: The results suggest the need to improve nutritional practices during hospitalization to enhance caloric delivery and reduce the risk of underweight. A multidisciplinary team including a pediatrician expert in nutrition may ensure close attention to adequate nutrition improving these patients' nutritional status.

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Human milk energy content of women donors in a human milk bank in Bogotá, Colombia is related with their socioeconomically factors

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**Aim:** To identify if the energy content of human milk from women donors of the USS Kennedy during 2016 in Bogota, Colombia, is related with some socioeconomically factors of the women.

**Methods:** The database registers of the women donors of the HMB of the USS Kennedy in Bogotá, Colombia during 2016 were used. Dependent variable was the energy content of human milk (colostrum, transition and mature), and independent variables were mother’s occupation, socio economical status, living place and offspring’s sex. Two statistical analyzes were carried out by SPSS and STATA software: A) analyzing each donation as an independent measurement and B) grouping the donations of each donor women by averages.

**Results:** 85 women 29.2 ± 5.7 years old, donors of the three human milk types. Most of them were professionals, living in stratum 3 and in Kennedy town, and 57% of their offspring were male sex. The energy content average of human milk donated was: 20.33 kcal/oz colostrum, 20.40 kcal/oz transition and 18.67 kcal/oz mature when the values were analyzed as independent measures, and when the values were analyzed by averages the energy content was: 20.33 kcal/oz colostrum, 20.53 kcal/oz transition and 19.16 kcal/oz mature. In turn, when the analysis type A was performed, a significant relationship between energy content of transition human milk and mother’s occupation was found (p=0.003) and with living place (p=0.006), as well as the energy content of mature human milk and all four mother’s socio economic variables analyzed (p<0.001). Nevertheless, the analysis of pooled measurements (analysis type B) none significant relationship was found (p>0.05).

**Conclusions:** The energy content of transition and mature human milk donated in the BMB of the USS Kennedy in Bogotá, Colombia during 2016 is related with socioeconomically factors of the mothers as occupation, socio economical status, living place and offspring’s sex.

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Quantification of total cholesterol in human milk by gas chromatography

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Objectives and Study: Human milk provides the key nutrients necessary for the infant growth and development. The objective of this study was to develop and validate a method to analyze the cholesterol content in liquid human milk samples along lactation.

Method: Direct saponification of the sample using ethanolic potassium hydroxide solution under cold conditions is applied and separation of unsaponifiable matter is carried out by centrifugation. Cholesterol is converted into trimethylsilyl ether and separation of cholesterol derivatives is performed by gas chromatography (GC) coupled with flame ionisation detector (FID). Finally, cholesterol is quantified using epicoprostanol as internal standard.

Results: The method has been validated by analysis of reference material showing good repeatability (CV(r)<15%) and good intermediate reproducibility (CV(iR)<15%). The method was applied to analyze human milk obtained from 5 mothers 30(±3), 60 (±3) and 120 (±3) days after delivery. The results showed that the cholesterol content in human milk slightly decreased from 13.1 mg/100g at 1 month to 11.3 mg/100g 120 days after delivery.

Conclusion: In this study a GC-FID procedure to quantify total cholesterol in human milk along lactation has been established and validated. This method has the advantages of robustness for the quantification of cholesterol in maternal milk comparing to the existing methods; the use of internal standard allowed proper quantification of analyte regardless sample preparation.

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Introduction: The terms small for gestational (SGA) and intrauterine growth restriction (IUGR) are often used synonymously in preterm infants. IUGR infants are newborns who failed to reach their potential growth due to a placental insufficiency, while SGA represents a constitutionally small infant. So far we do not consider the underlying pathogenesis in our treatment concepts, which might cause long-term consequences. Furthermore, the ESPGHAN recommends to feed enhanced nutrients up to 52nd week of gestation in all growth restricted preterm infants—regardless if they are SGA or IUGR. The aim of this study was to evaluate the effect of SGA and IUGR on growth and neurodevelopment in preterm infants.

Materials and methods: In a retrospective observational study all preterm infants born below < 10th percentile, < 32 weeks of gestation and < 1500 grams between the years 1999 and 2012 were included. The group assignment (SGA and IUGR) was based on prenatal pathological ultrasound measurements according to the Society for Maternal-fetal Medicine (SMFM). Preterm infants with genetic disorders affecting growth or neurodevelopment were excluded from the analysis. Anthropometric parameters were evaluated from birth until the age of 5½ years. Neurodevelopmental outcome was assessed by Bayley Scales of Infant Development at the corrected gestational age of 2 years and Kaufman Assessment Battery for Children (KABC) at the age of 5½ years.

Results: We included 158 preterm infants in this study, 31 SGA (19.6%) and 127 IUGR (80.4%). Median (interquartile range) birth weight was 600g (361-1240) in the SGA- and 688g (300-1215) in the IUGR-group (p=0.13), respectively. Median weight at term was significantly lower in the IUGR- (2530g) than in the SGA-group (3050g) (p=0.07), respectively. After term until the age of 5½ years, weight was lower in the IUGR- than in the SGA-group but did not reached significance. Weight catch-up growth (crossing 10th percentile) occurred earlier in the SGA- (6 month) than in the IUGR-group (4½ years). Length was significantly lower in the IUGR- than in the SGA-group at term (p=0.02) and at the age of 12 month (p=0.03). Length catch-up growth occurs earlier in the SGA- (6 month) than in the IUGR-group (2 years). No significant differences could be seen in the neurodevelopmental outcome.

Conclusion: Infants with different pattern of growth restriction (SGA and IUGR) showed different types of catch-up growth during the first years of life. These data indicates that the differentiation between SGA and IUGR are of major importance and IUGR preterm infants may need individual nutritional requirements to avoid growth restriction. Post discharged feeding recommendation for preterm infants should be adapted according to type of growth restriction.

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NUTRITION - Neonatal and infant nutrition

N-P-106

Changes in infant fecal pH shows a population-wide, generational loss of Bifidobacterium among breastfed infants over the last century

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Objects and Study: Bifidobacterium is thought to be the predominant genus in the breastfed infants gut, but several studies now question this assumption among breastfed infants in resource-rich countries compared to resource-poor areas. It is not clear whether these differences are the product of demographic differences, (including formula feeding, antibiotic usage, or cesarean section), genetic, or geographic differences between these populations. We previously showed that fecal pH is strongly associated with Bifidobacterium abundance in modern infants fed B. infantis EVC001, and reasoned that pH could provide a robust and rapid proxy for Bifidobacterium abundance when compared among historical records to address questions of Bifidobacterium abundance.

Methods: Using samples from healthy breastfed infants, we modeled fecal pH as a function of Bifidobacterium colonization, as determined by quantitative PCR. Then, we completed a meta-analysis of 15 clinical studies published between 1917 and 2016, representing more than 363 healthy breastfed infants where fecal pH was reported to model population wide Bifidobacterium abundances over the past century among healthy breastfed infants.

Results: Infant fecal pH was measured in these samples and fecal biochemistry was measured by mass spectrometry and used to model the relationship of lactate, acetate, and other short chain fatty acids as a function of fecal microbiome composition. Fecal pH was found to be a strong indicator of Bifidobacterium colonization and this was significantly correlative (P &LT; 0.001, Spearman's r = - 0.4801). From historic reports in the literature, nineteen study populations from 1917 to 2017 were used where pH was reported in healthy breastfed infants (n = 363). Mean infant fecal pH was found to steadily increase from pH 5 near 1900 to nearly pH 6.4 more recently. This was significantly correlated with time (adjusted $r^2$ = 0.973). These results suggest that Bifidobacterium was once more prevalent among infant populations than is reported today. Indeed, the pH reported from these samples matched the contemporaneous estimates of Bifidobacterium colonization when added to the modeled relationship between pH and Bifidobacterium.

Conclusion: The loss of highly specialized species, like Bifidobacterium longum subsp. infantis, may be an unintended consequence of modern medical interventions common among resource-rich nations; however, the loss of this keystone species loss should not be underestimated. Therefore, identifying infants that have lost this particular species is an important consideration when identifying interventions that restore this ecosystem to historical norms.

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Bifidobacterial abundance and prebiotics (HMOs, GOS and FOS) in infant nutrition

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Objectives and Study: Breast-feeding generally increases Bifidobacterial abundance in the infants' gut, which is one of the benefits of feeding breast milk compared to infant formula. A young infant's gut microbiome gradually establishes starting with the inoculum that the neonate received at birth. Exposure to the environment including the food leads to a continuous exposure to germs that may or may not establish in the infant's gut. The microbiome of the young infant's gut displays a relatively low diversity, but is subject to huge variations and fluctuations within the first months of life.

The feeding method and the presence of oligosaccharides in infant's nutrition in particular have an effect on positive selection of Bifidobacteria. Bifidobacteria can metabolize HMOs (human milk oligosaccharides); a group of sugars that are not or only slowly digested and taken up by the human host and that are in its abundance and spectrum unique to breast milk of humans and few related species. The spectrum of HMOs present in mother's milk especially with respect to the mother's secretor status modulates the Bifidobacterial composition of the infant's gut. Gut microbiomes of Formula-fed infants generally display a lower relative abundance of Bifidobacteria and have a higher microbial diversity. However, use of prebiotics in infant formula can increase the Bifidobacterial fraction in the infant's gut. Currently available prebiotics are Galacto- (GOS) and Fructo-oligosaccharides (FOS) that similarly to HMOs are metabolized by Bifidobacteria, but not by the human host. Unlike HMOs, GOS and FOS are not present in the natural infant's nutrition: their mother's milk. It has been demonstrated that within a limited set of bacteria 2'-Fucosyllactose, which represents the major HMO in secretors' breast milk, strongly enhances Bifidobacterium, whereas FOS used at the same concentration does not have the similar effect, suggesting that the kind of prebiotics make a huge difference.

Methods: Stool sample from a random set of young infants were collected in sample tubes and immediately frozen. DNA was prepared from stool samples, the V3-V4 of the 16S rDNA was amplified by PCR and the resulting pool of fragments was subjected to Next Gen Sequencing. The gut microbiome was determined by mapping the obtained sequences against a reference data base and calculating the fraction mapping against each entry.

Results: Our analysis of a random set of infant gut microbiomes reflects a high variance, which was expected when compared to most scientific publications on this topic. Furthermore, our study clearly shows that an individual gut microbiome cannot be solely predicted from the infant's nutrition and age, making it impossible to provide nutritional advises especially with the aim to increase the abundance of Bifidobacteria.

Conclusion: Our study demonstrates that the microbial composition of stool is barely predictable in infants, and even prebiotics enhancing growth of specific bacteria do not necessarily result in a higher abundance of those species. When indicated it might be beneficial to examine the microbial composition of infant stool to check if the gut microbial composition is within certain boundaries or if medical conditions can be related to imbalance or even the presence of pathogens.

Disclosure of interest: Marcus Ludwig and Stefan Jennewein are working for a supplier of human milk oligosaccharides as prebiotics.

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NUTRITION - Neonatal and infant nutrition

N-P-108

Complementary feeding practice in the Western Cape, South Africa

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Objectives and Study: A normal nutritional state is essential for the normal health and development of children. Though there is an increased awareness of the importance of exclusive breastfeeding and proper complementary feeding practice, there is marked variability in the rates and duration of breastfeeding in sub-Saharan Africa as well as the time of initiation, quality and adequacy of complementary feed. Poor complementary feeding practices are among the major contributors to the high burden of childhood malnutrition and mortality in the sub-Saharan Africa. Western Cape is a cosmopolitan city with people of diverse nationalities, socio-economic class, beliefs and cultural practices which could influence complementary feeding practices. The objective of this study was to describe the complementary feeding practices of caregivers of infants in the Western Cape.

Method: This cross-sectional descriptive study was conducted over a two month period of May 2017 to June 2017 in the out-patient unit of the Department of Paediatrics and Child Health, Tygerberg Academic Hospital, Western Cape Province of South Africa. One hundred and ten children aged six weeks to one year whose mothers or primary care giver gave consent were sequentially recruited into the study as they presented to the clinic. Data was obtained using a structured interviewer administered questionnaire. Data entry and analysis was done using SPSS version 20.1. A bivariate analysis was used to test for association and a p value less than 0.05 was considered significant. Ethical clearance was obtained from the Stellenbosch University Health Research Ethics Committee and the Tygerberg Academic Hospital.

Results: Of the 110 study participants, 1(0.9%) had an incomplete questionnaire and was excluded from analysis. There were 63 (57.8%) males and 46 (42.2%) females. Timely first suckling rate in the study population was 83 (76.1%) and ever breast fed rate was 79 (72.4%). Exclusively breastfeeding rate in the first six months of life was 8 (7.3%). Early introduction of complementary food before six months of age was 24 (22.0%) with cereals being the most implicated food. Juices were offered to 17 (5.5%) infants before six months of age, vegetables to 8 (7.3%), tea and sugar water to 6 (5.5%), white meat to 3 (2.8%), red meat to 1(0.9%) and chips to 3 (2.8%). Father's education was statistically significant with weaning practice of the study population, p-value=0.028.

Conclusion: The exclusive breast feeding rate in the study population was low. Early introduction of complementary feeds using non-nutritious and inappropriate food is still a problem in this region. There is the need for continuous education of care givers of children in the area on appropriate complementary feeding practices in view of its importance to the optimum growth and development of infants and young children.

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Gut microbial succession of preterm infants and full-term infants during the first 90 days of life

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Objectives and Study: Early colonization and development of the neonatal gut microbiome is critically important with a profound impact on the host lifelong health. The aim of this study was to obtain a longitudinal view of the gut microbial establishment of a cohort of 51 preterm (PT) infants compared to 50 full-term vaginally delivered (FTVD) infants from day 1 to day 90 after birth, and to identify key clinical factors that affect the establishment of neonatal microbiome.

Method: The microbial profile was examined by sequencing V3-V4 region of 16S rRNA amplicons of 581 faecal DNA. A random-effects generalized least square regression model was used to compare the difference of the main bacterial groups over time with the adjustment of multiple variables including gestational age and prophylactic antibiotics.

Results: Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes were the predominant phyla and accounted for more than 98% of total bacterial population in both PT infants and FT infants. PT infants harbored different gut microbial composition compared to that of the FTVD infants at genus level, with significantly higher level of Enterococcus (P&LT: 0.01), Acinetobacter (P&LT: 0.01) and significantly lower level of Bacteroides (P&LT: 0.01) colonized in PT group. Higher proportion of Escherichia-Shigella, Enterococcus and Acinetobacter were observed in the meconium samples compared to that of samples at any other time point for FT group during 90 days. The use of prophylactic antibiotics for mothers was positively correlated with the abundance of Enterococcus in FTVD group (P&LT: 0.01). Interestingly, the level of Escherichia-Shigella and Enterococcus was lower in the meconium but increased sharply by day 14-21 for PT group. Analysis of heat map revealed that the microbial profile between PT group and FTVD group clearly separated before day 70 but then clustered at 90 days of age. Gestational age was positively correlated with the abundance of Streptococcus (P&LT: 0.001) for PT group.

Conclusion: Our results suggested that PT group and FTVD group differed significantly with respect to the α-diversity and the main bacterial groups, especially at the first two months after birth. The use of prophylactic antibiotics and gestational age need to be considered for the analysis of infant microbiome.

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Infant behavior, breast milk composition at 6 weeks and breastfeeding outcomes at 6 months of age: A four country study

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Objectives and Study: Few studies have investigated factors influencing infant behavior such as cultural practices or the impact of infant behaviour on breast-feeding. We aimed to (i) describe + examine predictors infant behaviour at age 6 weeks (6w) in 4 countries, 2 where traditional confinement practices were followed; & ii) explore associations between infant behavior + breast milk composition at 6w + infant feeding at 6 months (6mo).

Method: Data collected from 174 exclusively breastfeeding (EBF) mothers + their healthy term infants recruited from the UK(n=50), China(n=45), Russia(n=46) + Malaysia(n=33) as part of 2 prospective studies. At 6w post-partum, mothers completed a 3-day infant behaviour diary recording time sleeping, feeding, crying (incl cry, fuss & colic) or awake & happy (A&H). Fore- + hindmilk samples were collected at 6w from mothers in the UK + Malaysia; fat, protein, carbohydrate + energy content were measured by an infra-red analyser. Infant feeding method was recorded at 6mo (categorised as EBF, mainly BF +/- complementary feeding (CF), mainly formula fed +/- CF) by mothers in the UK, China + Russia.

Results: Infant behaviour: Maternal age was positively correlated with crying time (r=0.25, p=0.001) + negatively with time A&H (r=-0.23, p=0.003) at 6w. First-born infants spent significantly longer periods A&H (298(SD126) v 253(93)mins/24hr, p=0.02)) + shorter periods asleep than non first-born infants (843(137) v 898(119), p=0.02). Birthweight (Bwt) was not correlated with behaviours . Behaviour differences were apparent between countries even after adjusting for parity, maternal age + Bwt (Table). Chinese infants had the longest sleep times (significantly greater than UK or Malaysia). By contrast, Malaysian infants spent significantly longer periods A&H compared to other sites, with significantly lower sleep time than Chinese infants + shorter crying time than UK or Russian infants. Russian infants had the shortest feed time, significantly lower than UK or Chinese infants. Breast milk composition + infant behaviour. Hindmilk fat + energy from UK mothers was significantly higher than Malaysian mothers after adjusting for confounders (fat: 6.5(0.4) v 4.9(0.4)g/l, p=0.01; energy: 94.0(3.9) v 78.0(3.9)kcal/l, p=0.01). These differences did not explain differences in A&H time between UK + Malaysian infants (adv’d means 282(25) v 382(31) mins/24hours, p=0.02), but differences in crying were no longer significant after adjustment for hindmilk fat or energy (adv’d means UK 82(SE14) v Malaysia 39(16) mins/24hours (p=0.06)).

Behaviour at 6w + feeding at 6mo. Infant behaviour and demographic factors at 6w were not significant predictors of infant feeding at 6mo. In UK mothers (n=22), breast milk composition at 6w did not predict infant feeding at 6mo.
<table>
<thead>
<tr>
<th>County</th>
<th>Sleeping</th>
<th>Feeding</th>
<th>Awake + Happy</th>
<th>Crying (including fussing + colic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mins/24hr (mean(SE))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK (n=50)</td>
<td>851 (19)</td>
<td>218 (11)</td>
<td>270 (16)</td>
<td>102 (11)</td>
</tr>
<tr>
<td>Malaysia (n=33)</td>
<td>826 (26)</td>
<td>200 (15)</td>
<td>366 (23)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Russia (n=46)</td>
<td>891 (19)</td>
<td>183 (11)</td>
<td>277 (17)</td>
<td>89 (11)</td>
</tr>
<tr>
<td>China (n=45)</td>
<td>923 (23)</td>
<td>231 (13)</td>
<td>216 (20)</td>
<td>69 (13)</td>
</tr>
<tr>
<td><strong>Time Sleeping</strong></td>
<td>China &gt; Malaysia, p=0.002; China &gt; UK, p=0.01.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time Feeding</strong></td>
<td>Russia &lt; China, p&lt;0.01; Russia &lt; UK, p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time Awake + Happy</strong></td>
<td>Malaysia &gt; China, p&lt;0.001; Malaysia &gt; UK, p=0.001; Malaysia &gt; Russia, p=0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time Crying</strong></td>
<td>Malaysia &lt; UK, p&lt;0.01; Malaysia &lt; Russia, p=0.04</td>
<td></td>
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</tr>
</tbody>
</table>

**Conclusion:** Significant differences in infant behaviour at 6w were apparent between countries, even after adjusting for confounders. It is possible that the more 'positive' behaviours reported in Malaysian + Chinese infants (longer periods asleep or A&H) reflect infant care practices resulting from traditional confinement periods; this merits further exploration. We found no consistent associations between infant behaviour or milk composition at 6w + infant feeding at 6mo, but this requires investigation in a larger sample.

**Disclosure of interest:** Data collection in China, UK and Russia was supported by a grant from Philips Avent, Philips Center, Amstelplein2, 1096BC, Amsterdam, The Netherlands. MF and KK receive an unrestricted donation from Philips Avent, Philips Center, Amstelplein2, 1096BC, Amsterdam, to carry out research in infant feeding.

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Attitudes and current practices in complementary feeding of Thai urban families

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Objectives and Study: Urban families in middle-income countries are currently facing cultural and lifestyle transition. Changing from agricultural to industrial societies may affect family roles and childcare practices. Despite improvements in education, reduced poverty and affordable healthcare, these countries face the double-burden of under- (energy and micronutrients deficiency) and over-nutrition (increased obesity risk). The present study aims to describe family attitudes and practices in terms of complementary feeding in this situation.

Method: A cross-sectional study was conducted in three Child Health Clinics in Chiang Mai, Thailand. Self-administered questionnaires were given to families who take care of healthy infants and children ages 6 to 18 months old during October to November 2016.

Results: One-hundred and eight respondents completed questionnaires. The study found different attitudes and knowledge gaps between the respondents who were mothers and other family members. The ‘other’ respondents were less likely to value complementary feeding as a crucial factor promoting child growth and development. Moreover, they had misperceptions about the benefits of animal-based protein and were less confident in their ability to feed the child properly. Most families reported timely introduction of complementary food, using appropriate milk products as well as encouraging age-appropriate self-feeding and drinking. However, there were undesirable practices including delaying introduction of animal-based protein, inadequate food diversity, the use of seasoning, feeding premasticated food and offering food as a reward.

Conclusion: These findings suggest nutritional education should be extended to all caregivers involved in complementary feeding to improve the adherence to feeding recommendations.

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Electrolyte abnormalities in preterm neonates receiving electrolyte-free versus standard parenteral nutrition solutions: a two-centre retrospective study

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Objectives and Study: There is current debate as to whether “electrolyte-free” parenteral nutrition (PN) solutions should be used for preterm infants during the first days of PN provision. Electrolyte-free PN does not contain Na⁺, K⁺, Cl⁻, Ca²⁺, PO₄, or Mg²⁺ and is preferred by some to restrict early sodium intakes during the postnatal transitional period of extracellular fluid contraction and physiological weight loss. Yet sufficient early electrolyte supplementation is needed for adequate protein accretion when delivering higher amounts of amino acids. In the East of England region of the U.K., some centres routinely use electrolyte-free PN while others use electrolyte-supplemented PN from birth. We compared the incidence of electrolyte disturbances of Na⁺, K⁺, Ca²⁺ and PO₄ in preterm infants according to whether they received electrolyte-free PN or standard (electrolyte-supplemented) PN. Our hypothesis was that there would be no difference in incidences of hypernatraemia or hyperkalaemia during the first postnatal week.

Method: This was a retrospective cohort study done at two UK tertiary-level neonatal units. Centre 1 routinely uses electrolyte-free PN in the first 48-72h after birth, while centre 2 routinely uses standard PN. We included preterm neonates <36 weeks' gestational age who started on PN within 24 hours of birth within two discrete 6-month epochs. Outcome measures were first-week peak and nadir serum Na⁺, K⁺, Ca²⁺, and PO₄ concentrations; and proportions with hypernatraemia (Na⁺ >150 mmol/L), hyponatraemia (Na⁺ < 130 mmol/L), hyperkalaemia (K⁺ >7.0 mmol/L), hypokalaemia (K⁺ < 3.5 mmol/L), hypercalcaemia (Ca²⁺ >3.0 mmol/L), and hypophosphatemia (PO₄ < 1.5 mmol/L).

Results: A total of 81 patients (n=43 centre 1; n=38 centre 2) were included. Median (IQR) gestational age was 27.1 (25.7-29.2) weeks and mean (SD) birth weight was 986 (321) g, with no significant demographic differences between centres. More babies who received electrolyte-free PN in the first week (centre 1) had hyperkalaemia (12% vs 0%, p=0.03), hypernatraemia (28% vs 3%, p=0.001), hypokalaemia, (77% vs 40%, p=0.001), and hypophosphataemia (81% vs 37%, p=0.002) compared with standard PN babies (centre 2). Nadir Na⁺, K⁺, and PO₄ concentrations were also significantly lower in babies who received electrolyte-free PN. Comparative rates of hypernatraemia (16% vs 34%, p=0.06), hypercalcaemia (18% vs 21%, p=0.8), and median peak Na⁺ (147 mmol/L vs 148 mmol/L, p=0.6) and Ca²⁺ (2.9 mmol/L vs 2.8 mmol/L, p=0.3) concentrations were similar.

Conclusion: Use of electrolyte-free PN within the first 2-3 days after birth was not associated with significantly lower rates of first-week hypernatraemia, but was instead associated with higher rates of hyponatraemia, hyperkalaemia, hypokalaemia and hypophosphataemia. Routine use of electrolyte-free PN solutions may not be optimal for preterm neonates in the first week.

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Neonatal modulation of gut digestion, microbiota and physiology by addition of dairy lipids and probiotic L. fermentum in infant formulas

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Objectives and Study: Breast milk is the gold standard in neonatal nutrition but most infants are at least partly formula-fed. Breast milk complex lipid matrix and diversified bacterial ecosystem may be key factors in the interplay between gut microbiota and host physiology. However, few infant formulas (IF) contain dairy lipids (DL) but rather plant lipids (PL), and some contain a probiotic component. The objective of this study was to investigate, in a Yucatan minipig model, the effects of the addition of both DL and a probiotic strain isolated from breast milk (Lactobacillus fermentum CECT 5716, Lf) in IF on digestion, gut physiology and microbiota.

Method: Piglets received from postnatal day 2 to 28 a balanced formula containing either only plant lipids (PL, n=9), a half-half mixture of PL and DL (DL, n=9), or a half-half mixture of PL and DL supplemented with Lf (DL+Lf, n=8). They were euthanized at PND28 to investigate the effects of IF composition on digestion (proteolysis and lipolysis), intestinal microbiota composition (16S rRNA sequencing) and metabolism (¹H NMR metabolomic analysis), intestinal physiology (barrier and endocrine functions) and their relationship with the endocrine pancreas development.

Results: DL(±Lf) led to an increased IF gastric proteolysis compared to PL. For all diets, peptide diversity was the highest in stomach, decreased by more than half in proximal jejunum and by more than 95% in median jejunum, ileum and colon. In stomach and proximal jejunum, peptides mainly originated from beta-casein (38-49%), beta-lactoglobulin (23-25%) and alpha-s1 casein (~13%). Peptide diversity in colon was lower in PL compared to DL(±Lf). IF ileal lipolysis was also increased in DL(±Lf) compared to PL. Accordingly, DL(±Lf) displayed lower plasma triglycerides and free fatty acids concentrations compared to PL. Moreover, faecal microbiota composition and metabolism were different between groups, with 6 discriminating genera between PL and DL(±Lf) as well as 20 metabolites such as valerate, lysine and glucose. This was associated with changes in intestinal barrier function. Compared to PL, DL+Lf led to an increased number of goblet cells in jejunal villi and DL(±Lf) decreased colon transcellular permeability, to values similar to those observed in sow-reared piglets. Endocrine pancreas was significantly more developed in DL compared to DL+Lf independently of any change in intestinal GLP-1 secretory capacity. Ongoing systems biology approach will help to understand relationships between IF composition, microbiota and host physiology. Strong correlations between gut microbiota and host physiology have already been highlighted: several Alloprevotella species, that were more abundant with DL(±Lf), were correlated to the presence of several metabolites (negatively to total caecal short-chain fatty acids and glycerol and positively to lysine), to colon transcellular permeability (negatively) and to the endocrine pancreas (positively).

Conclusion: This work clearly demonstrates that the addition of dairy lipids and probiotic L. fermentum induced changes in gut digestion and physiology in relation to modulation of microbiota composition and metabolism. This may help to decrease the physiological gap between breast milk and infant formulas.

Disclosure of interest: This study was supported by Lactalis. The authors whose names are listed below report a conflict with Lactalis: M. Lemaire, P. Le Ruyet, I. Cuinet and C. Baudry.

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Can intestinal microbiota modulate body composition of late preterm infants?

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Objectives and Study: The intestinal microbiota derives from the early environment but can influence health and disease of human host during life. It has been demonstrated that Streptococcaceae families are associated with an increase BMI. Late preterm infants, born from 34 to 36 weeks gestational age (GA), experience an altered growth characterized by an increased adiposity at term corrected age compared to full term infants. The aim of the study was to explore the role of intestinal microbiota in modulating body composition of late preterm infants from birth to term corrected age.

Method: Singletons late preterm infants born at Author's Institution were enrolled at birth. Anthropometric measurements (weight, length and head circumference) and body composition in terms of fat mass (FM) were assessed on the 5th day of life and at term corrected age using an air displacement plethysmography (Pea Pod Infant Body Composition System, Cosmed, Italy). Delta FM was computed as the difference between FM at term corrected age and FM on the 5th day of life. At each study point, type of feeding was recorded and categorized as being feeding any human milk or being feeding exclusive formula. At the same study points stool samples were collected for microbiota analysis (Bioinformatic analysis of Metagenomic AmpliconS). A Principal Coordinate Analysis (PCoA) based on Bray-Curtis dissimilarity matrix was conducted to investigate the bacterial families according to the study points, the type of feeding and the mode of delivery. Pearson's correlation tests were also conducted to explore the association between bacterial families and body composition.

Results: Thirty-three late preterm infants were enrolled. Mean GA and weight at birth were 35.3±0.8 weeks and 2419±394 g, respectively. A total of 63.6% was born by caesarian section and 42.4% were males. Any human milk was received by 79% of infants on the 5th day of life and by 73% at term corrected age. Anthropometric measurements and body composition on the 5th day of life and at term corrected age are shown in the table. Delta FM was 327.2±184.2 g.

<table>
<thead>
<tr>
<th></th>
<th>5th day of life</th>
<th>Term corrected age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>2377.1±263.1</td>
<td>3302.5±448.2</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>45.0±1.6</td>
<td>49.5±1.9</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>32.1±0.9</td>
<td>34.8±1.1</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>111.4±98.7</td>
<td>425.9±188.8</td>
</tr>
</tbody>
</table>

Different clustering patterns of bacterial families have been found on the 5th day and at term corrected age. No differences were found according to the type of feeding and the mode of delivery. Anaerolineaceae and Streptococcaceae families were associated with FM (r: 0.45, p< 0.001 and r: 0.57, p< 0.05 respectively) whereas Peptostreptococcaceae were associated with delta FM (r: 0.61, p< 0.001).

Conclusion: Late preterm infants exhibit an early major increase in fat mass which appears to be associated with the Streptococcaceae families. Larger studies are necessary to confirm these preliminary results.

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The effect of deep freezing on human milk macronutrients content

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Objectives and Study: Long term storage of human milk (HM) requires freezing at low temperatures, the consequences of which upon macronutrients are unclear. There are only few studies on freezing-induced changes in HM nutrients concentration with conflicting results leading to different storage recommendations. We aimed to examine differences in macronutrients content of long-term stored HM at -20°C versus -80°C.

Method: Samples of mature expressed HM were collected from 25 mothers of preterm and term infants at mid expression using a commercial breast milk pump (Medela, Baar, Switzerland). Immediately following extraction each sample was divided into six aliquots of 3 ml each: three aliquots for storage at -20°C (storage duration of 4, 12, 24 weeks) and three aliquots for storage at -80°C (storage duration of 4, 12 and 24 weeks respectively), for a total of 150 aliquots. The fresh expressed milk aliquots were stored in hospital/home refrigerator at 4°C for a maximum period of 24 hours before being transferred for long term storage at -20°C and -80°C. At strict time frames (4, 12, 24 weeks), each sample was thawed, homogenized and analyzed for macronutrients content. Thawing was performed by heating the aliquots at 40°C in a thermostatic bath, and homogenization was obtained by ultrasonification. Macronutrients and energy contents were measured using HM analyzer (Miris, Upsala, Sweden), an instrument based on mid-infrared transmission spectroscopy.

Results: A total of 150 aliquots were analyzed. Thirteen samples were removed due to calibration error. The final analysis was performed on 137 samples with validated results. Fat and energy contents were consistently higher in the -80°C samples compared with the paired -20°C samples at each of the time points (p< 0.05). Comparing the differences in macronutrients content over time (4 weeks versus 24 weeks) revealed a significant loss of fat (0.3 g/100 ml (=7.9%), p=0.001) and energy (2.3 kcal/100 ml (=3.3%), p=0.03) in the -20°C group (table). In the -80°C group, fat and protein were found to be significantly decreased over time (fat: 0.14g/100 ml (=3%), p=0.009; protein 0.06g/100 ml (=6.4%), p=0.02).

<table>
<thead>
<tr>
<th></th>
<th>-20°C group (n=68)</th>
<th>-80°C group (n=68)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (g/100 ml)</td>
<td>4.0±1.0</td>
<td>4.3±1.0</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Carbohydrates (g/100 ml)</td>
<td>7.6±0.3</td>
<td>7.6±0.3</td>
<td>0.723</td>
</tr>
<tr>
<td>Protein (g/100 ml)</td>
<td>0.95±0.28</td>
<td>0.95±0.25</td>
<td>0.933</td>
</tr>
<tr>
<td>Energy (Kcal/100 ml)</td>
<td>68.5±7.6</td>
<td>71.4±7.9</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Conclusion: Long-term storage of human milk at -80°C is associated with fat and energy preservation compared to storage at -20°C. The results of our study may help construct evidence based recommendations and guidelines for HM storage.

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Objectives and Study: The medical literature describes significant differences in morbidities between males and females, in infancy and throughout childhood and beyond. However, little is known about the effect of the infant’s gender on human milk (HM) macronutrients content. We designed the current prospective observational study to examine differences in macronutrients and energy content of HM expressed from mothers to male newborns as compared to mothers of female newborns. We hypothesized that no differences in macronutrient content would be found between HM expressed for both genders.

Method: Samples of expressed HM were collected from 322 mothers of preterm and term infants (26 to 42 weeks gestation) at mid expression using a commercial breast milk pump (Medela, Baar, Switzerland). Each mother contributed 3 samples of HM, the first during the 72 hours after labor (colostrum), the second after 7 days (transitional HM) and the third after 10-14 days post partum (mature HM). Immediately following extraction, samples were stored in a refrigerator at < 5°C for a maximum period of 24 hours before being transferred for long term storage at -20°C. Just before analysis, thawing was performed by heating the aliquot at 40°C in a thermostatic bath, and homogenization was obtained by ultrasonification. Macronutrients and energy contents were then measured using HM analyzer (Miris, Upsala, Sweden), an instrument based on mid-infrared transmission spectroscopy.

Results: Recruited were 322 women of which 161 were mothers to male and 161 were mothers to female newborns. A total of 601 HM samples were collected (247 colostrum samples, 159 transitional HM samples and 195 mature HM samples). Maternal age was 33±2.4 years (range: 20-43), mean gestational age was 38.3±2.8 weeks (range: 26-42) and mean birthweight was 3087±724 g (range: 588-4505).

Macronutrients and energy contents of colostrum and transitional HM samples were similar for both gender. However, the mean protein content of mature HM was significantly higher in samples obtained from mothers of female newborns than in those obtained from mothers of males (1.11±0.62 g/100 ml and 0.93 ± 0.43 g/100 ml, respectively, p< 0.028, table).

<table>
<thead>
<tr>
<th></th>
<th>HM From Mothers to Females</th>
<th>HM From Mothers to Males</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/100ml)</td>
<td>1.11±0.62 (0-3.6)</td>
<td>0.93±0.43 (0.1-2.1)</td>
<td>67.21±18.2 (21-109)</td>
</tr>
<tr>
<td>Protein (g/100ml)</td>
<td>5.65±1.58 (2.5-8.8)</td>
<td>5.29±1.59 (1-7.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fat (g/100ml)</td>
<td>4.12±1.7 (0.3-8.8)</td>
<td>4.36±1.58 (0.7-10.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Energy (Kcal/100ml)</td>
<td>67.21±18.2 (21-109)</td>
<td>66.38±17.4 (11.5-118)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Conclusion: Protein content in mature HM is higher in HM samples obtained from mothers of female newborns as compared to mothers of males. No differences in HM macronutrients content were found in colostrum and transitional HM samples. The mechanism and the physiological and clinical significance of our finding is yet to be determined.

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The current practice of exclusively breast-feeding and complimentary feeding in the Belgorod region

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Objectives and Study: This investigation is aimed to study the features of feeding children of the first year of life, especially different aspects of complementary feeding in the Belgorod region.

Method: We conducted a survey of 348 women with children aged 1 to 4 years (boys - 166 / 47.7% and girls - 182 / 52.3%). The main sections of the questionnaire included questions that characterize woman’s nutrition during pregnancy, the nature of feeding, the duration of breastfeeding, the time of introduction of complimentary feeding and the range of products used. Criteria for inclusion in the study: women with young children (from 1 to 4 years of age) who were born healthy on the 38-41 week of gestation.

Results: It was shown that a high percentage of mothers (half of the women surveyed - 180 / 51.7%) did not follow a balanced diet during pregnancy. The duration of breastfeeding in 50% of cases was prolonged (more than 8 months), at the same time in 29.8% of cases there was an early transition to artificial feeding (until the child reaches the age of 3 months).

Information about the peculiarities of introducing of complementary foods mothers in 60% of cases received from the local doctor. In other cases women were guided by various sources, among them the Internet (18%), then relatives and friends (13%) and others. The greatest number of errors related to the timing of the introduction of complementary foods (previously 4 months and later 6 months it was introduced for 22% of children), the rules of introduction (52.7% of mothers introduced complementary feeding between feedings, after feeding "for dessert" and when it was convenient). Assessment of the features of physical development and the frequency of detection of pathological conditions in children by 12 months of life showed that deviations from the average body mass index (BMI) were detected in 31.5% of children (in 17.5% of cases there was a deficiency in body weight and in 15% - an excess of body weight). In addition, 177 / 50.8% of children have different pathological conditions, among which the leading positions are occupied with food allergy (56%).

Conclusion: Based on a questionnaire survey of 348 parents of children from 1 to 4 years of age, were identified the follow feeding problems: later application to the breast (44%), early transition to artificial feeding until the baby reaches the age of 3 months life (29.8%). There were significant violations in the technique of complementary feeding. It is necessary to continue to implement the current recommendations on feeding in daily practice.

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Association of breast-feeding on weight loss, urinary and stool passage and bilirubin level

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Objectives and Study: Urinary and defecation frequency have correlation with hydration and breastmilk adequate intake in neonates, therefore it can be used as an indicator of weight loss. However excessive weight loss is one of risk factor of hyperbilirubinemia. The global strategy for infant and young child feeding stated for early and exclusive breastfeeding during the first 6 months. Despite the many advantages of breastfeeding, some reported about the dehydration, poor body weight gain, and hyperbilirubinemia in breastfed infant are more common. The objective of the study was to evaluate the influence of breastfeeding to the frequency of urinary and stool passage, the weight loss and jaundice in the first week of life.

Method: This was a longitudinal study by using medical records of neonates born in one hospital in Semarang Indonesia. The inclusion criteria were full term and vigorous babies, no congenital anomaly, and got rooming-in with their mothers. Data of eight loss, urinary and stool passage frequency were collected during the first week of life. Bilirubin level was examined at the third day. Statistic analysis used Mann-Whitney, Spearman correlation, and chi square for asses the risk factors.

Results: There were 466 healthy mother-neonate pairs (54.7% boys and 45.3% girls). The exclusively breastfed was 59.6% babies. The mean birthweight was 3167±334 g. On the third day, the exclusive breastfed babies has lesser on urinary (5.0±2.16 vs 6.5±2.62; p<0.001), stool passage (4.2±2.0 vs 5.6±2.38; p<0.001), but the weight loss percentage was greater (6.9±1.69 vs 6.3±2.49; p=0.008). However the bilirubin level was higher on the non exclusive breastfed (8.9±2.94) than exclusively breastfed (8.1±2.27) p=0.013. There was positive correlation between weight loss and bilirubin level (r=1.33; p=0.001. And the exclusive breastfeeding is the protector for getting hyperbilirubinemia (stated as total Bilirubin ≥ 12.0 mg/dl) with OR 0.44 (95% CI 0.18-0.66; p=0.001).

Conclusion: There was positive correlation between weight loss and bilirubin level. Exclusive breastfeeding is the protector for getting hyperbilirubinemia in fullterm neonates during the first week of life.

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The correlation of maternal protein intake during third trimester of pregnancy with fetal weight gain

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Objectives and Study: Prenatal exposure to dietary protein may program growth regulating hormones, influencing early-life growth patterns and later risk of non communicable disease in adulthood. The insulin-like growth factor 1 (IGF-1) has role in influence of prenatal and infant growth and its sensitivity to the early nutritional environment. Our purpose of ongoing cohort study is to examine the associations of maternal protein intake from third trimester of pregnancy with fetal and infant growth until six month of life, IGF-1 and leptin level. We reported our first preliminary study about the association of maternal protein intake with the fetal growth.

Method: This was a cohort study with subjects were 48 mother-child pairs from third pregnancy through delivery. The inclusion criteria were healthy mothers with singleton pregnancy, and their offspring were fullterm and vigorous baby, no asphyxia and no congenital anomaly. We measured the estimated fetal weight (EFW) by ultrasound, maternal protein intake by 3-days food recall and compared with Indonesian Reference Nutrient Intake (RNI). To calculate the fetal weight gain we used the percentile of Intergrowth 21\textsuperscript{st} growth standard. Statistic analysis used spearman correlation.

Results: The mean age of mothers was 28±5.9 years, height 155±5.2 cm. The mean gestation for ultrasound examination was 33±2.1 weeks and EFW 2071±325.1 g. The mean gestation when the babies born was 39±1.6 weeks, birthweight 3064±347.4 g and length 48.7±1.59 cm. The protein intake during third semester 53.9±14.57 g (86.9% compared to Indonesian RNI). The fetal weight gain was 23.8±12.93 g/d. By using the Intergrowth 21\textsuperscript{st} standard we calculated that the percentile of EFW was 54.7±29.42 and the percentile of birthweight was 37.8±28.85, thus it was decrease -16.9±33.15 percentile. There were a significant correlation between EFW and birth weight ($r=0.33; p=0.021$) and birth length ($r=0.57; p<0.001$) and negative correlation between maternal protein intake with fetal weight gain ($r=-0.30; p=0.04$).

Conclusion: In pregnant women with relatively high mean protein intakes, higher intake was associated with lower fetal weight gain.

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Objective and Study: There is no definitive curative treatment for NEC, many treatments are widely investigated one of these investigated lines is the use of hematopoietic factors to improve NEC especially erythropoietin (EPO), based on the finding that fetus swallows amniotic fluid which contains several growth factors that are also present in breast milk, EPO has given enterally is believed to affect the growth of villi and crypts, decreases the inflammatory mediators in the gastrointestinal tract resisting injury, and also protects the intestinal barrier function. The aim of this longitudinal prospective double-blinded controlled study was to evaluate the effects of enteral administration of recombinant human erythropoietin (rh EPO) in preterm infants born 32 weeks of gestation or less and to determine whether oral erythropoietin decreased feeding intolerance or had prophylactic effect against NEC.

Materials and methods: An interventional randomized control trial was conducted on 120 preterm infants born less than or equal 32 weeks gestational age admitted to neonatal intensive care unit at; 60 cases were randomly received rh EPO while the other 60 were received Placebo. Erythropoietin administration or placebo was started with the start of feeding and was discontinued when the patient’s enteral intake reached 150 mL/kg or after a maximum of 10 days. 63 patient dropped from both groups due to either the intake of enteral hematopoietic growth factor intravenous immunoglobulin or due to their early death before the completion of the drug treatment days,57 preterm infants remained after the exclusion:32 preterm infants in the EPO group and 25 preterm infants in the placebo group.

Results: Our study showed no significant decrease in the incidence of vomiting or other signs of feeding intolerance as presence of gastric residuals, abdominal distension or the incidence of NEC in rh EPO group compared to the placebo group; the rh EPO group demonstrated no significant difference in the day of start of enteral feeding, the time to achieve one-half (75 mL/kg/day), two-thirds (100 mL/kg/day) and full enteral feeding (150 mL/kg/day), with no significant decrease in the incidence of vomiting or other signs of feeding intolerance as presence of gastric residuals, abdominal distension or the incidence of NEC compared to the placebo group. The duration of withholding feeding secondary to feeding intolerance, weight gain or hospital stays were not significantly different between both groups group

Conclusions: Erythropoietin as a trophic factor does not appear to affect feeding intolerance or NEC incidence.

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Effect of aggressive versus standard nutritional regime on growth of extremely low birth weight infants - a randomized controlled trial

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Objectives and Study: Early aggressive nutrition reduces cumulative caloric and protein deficits and may improve growth parameters in extremely low birth weight (ELBW) infants. To compare growth parameters at discharge in aggressive nutritional (AN) regime vs standard nutritional (SN) regime.

Method: In a pilot study, 22 infants were randomized. Infants were assigned to either to 1. AN regime - higher amino acid (3g/Kg/d) and lipids (3g/kg/d) on day 1, parenteral nutrition discontinued at 160 ml/kg/day of feeds and fortification of human milk initiated at 25 ml/kg/day of feeds or 2. SN regime - incremental amino acids and lipids, parenteral nutrition discontinued at 100 ml/kg/day feeds and fortification initiated at 100 ml/kg/day of feeds.

Daily weight, and weekly length and occipito-frontal circumference (OFC) were measured

Results: The mean (SD) weight and gestation of enrolled infants were 839.55 (142.88) g and 28.3 (2.38) weeks respectively. The mean (SD) protein intake in AN regime on day 1 and 2 was significantly higher as compared to SN regime; 3.1 (0.42) and 3.86 (0.54) vs 2.39 (0.95) and 2.96 (0.97) g/kg/d, P value- 0.042 and 0.018 respectively. The mean (SD) calorie intake in AN vs SN regime on day 1 and 2 were 72.22 (15.55) and 88.62 (9.3) Cal/kg/d vs 47.34 (11.1) and 60.3 (21.5) Cal/kg/d, P value- 0.000 and 0.001 respectively. At discharge, there was no difference in weight growth velocity, length increment and OFC gain in AN regime vs SN regime-[10.92 (4.6) g/kg/day vs 10.51 (5.7) g/kg/day, 0.47 (0.11) cm/week vs 0.59 (0.24) cm/week and 0.65 (0.22) cm/week vs 0.77 (0.27) cm/week, P values-0.86, 0.20 and 0.33 respectively]. There was no difference in other clinical outcome such as BPD, NEC, Sepsis and mortality.

Conclusion: Aggressive nutritional regime does not improve growth parameters in ELBW infants as compared to standard nutritional regime.

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Breast feeding patterns: experience in Alexandria, Egypt

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Objective and Study: WHO and UNICEF's global recommendations for optimal infant feeding are: initiation of breastfeeding within the first half an hour after birth, exclusive breastfeeding for 6 months (180 days) and nutritionally adequate and safe complementary feeding starting from the age of 6 months with continued breastfeeding up to 2 years of age or beyond. The objectives of the study were to reveal the rate of exclusive and predominant breast-feeding in infants up to 6 months, the rate of the proper time of introducing the complementary feeding and its adequacy in infants, the rate of continued breast-feeding at one year, the rate of bottle-feeding for infants less than 12 months in one year old infants at Alexandria primary healthcare centers

Methods: Descriptive cross sectional approach was selected to achieve the study objectives using interview questionnaire for 300 mothers of one year old infants who had attending different primary healthcare centers for obligatory MMR vaccine.

Results: As regard the rate of exclusive breastfeeding, 12% of the studied infants were exclusively breastfed up to the age of one month. By the age of two months, the exclusive breastfeeding rate decreased to (11%). At three and four months, the rates were (10% and 7%) respectively. Another drop occurred to reach (4%) at the age of five months. Only (3%) of the studied mothers achieved WHO recommendations and exclusively breastfed their infants for six months. The predominant breastfeeding was 28 % up to 6 months. Formula feeding rate up to 6 months was 62%, the rate of bottle feeding in infants 0-12 months was 92% and the rate of breastfeeding continuation up to one year was 74%. The rate of timely introduction of complementary foods was 24%, infants had non-adequate complementary food were 66 %.

Conclusion: This study revealed that the rate of exclusive breastfeeding in Egypt was found to be low the rates of formula feeding and bottle feeding were high, the rates of timely introduction of complementary feeding and its adequacy were low.

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Naturally high content of nucleotides in goat milk based infant formula

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Objectives and Study: Nucleotides from dietary sources have been suggested to have important physiological roles in immune function, gastrointestinal development and metabolism. Goat milk contains considerable amounts of nucleotides but little data is available on nucleotide content in goat milk infant formula (IF) and follow-up formula (FOF). Furthermore, nucleotide concentrations in bovine and human milk decrease with advancing lactation but it is unknown whether seasonal variation also occurs in goat milk.

The aim of this study was to quantify the level of total nucleotides in goat milk IF and FOF versus cow milk formulas. The second objective was to study seasonal variation in levels of free 5´-monophosphate nucleotides in skimmed goat milk powder, the basis for goat milk formula.

Method: Total nucleotide levels were measured by liquid chromatography in goat and cow milk IF and FOF. Nucleotides in excess of supplemented amounts were assumed to be naturally occurring nucleotides. Additionally, individual free 5´-monophosphate nucleotide levels were determined in skimmed goat milk powder at several time points throughout the year.

Results: Formulas based on goat milk have 40-50% higher naturally occurring levels of total nucleotides than cow milk based formulas. Uridine 5´-monophosphate was the major nucleotide in skimmed goat milk powder. In addition, a natural variation in AMP and UMP content was seen with levels around 4-6 times higher in April (coinciding with the early lactation period) as compared to early winter.

Conclusion: Skimmed goat milk powder, goat milk based infant formula and follow-up formula contain high levels of nucleotides. In addition, seasonal variation in free nucleotide levels in skimmed goat milk powder was observed. Future research should determine individual free nucleotide levels in goat milk during the different stages of lactation and ultimately in goat milk IF and FOF.
**Compounding individualised paediatric parenteral nutritions during the week-end: how to optimise the process?**

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**Objectives and Study:** Individualized compounding of parenteral nutrition (PN) is proposed for daily adaptation in our institution for neonates and children. This possibility offered to clinicians to daily adapt the formulation has a high impact on the pharmacy compounding and quality control laboratory. Due to the week-end daily prescription the pharmacy has a heavy workload and high costs. To analyse if individualized PN prescribed and produced every day during the week-end has a clinically significant relevance because of changes in the formulation justifying a daily compounding in the pharmacy during the week-end.

**Methods:** Retrospective study of all week-end compounded PN (Friday to Sunday) during two 8-months periods (March to October 2015 and March to October 2016) with implementation of nutrition’s teaching program in 2016 proposed to all prescribing clinicians in the institution.

PN prescription sequences of at least 3 days were selected and defined in 2 categories:
- unplanned = PN prescribed every day during the week-end
- planned = PN prescribed on Friday for 3 days

Clinically significant day-to-day formulation changes were defined with a neonatologist and a paediatrician gastroenterologist as a change of at least: glucose>±2 mg/kg/min and/or amino acids>±1g/kg/24h, sodium>±2.0 mmol/kg/24h, potassium>±1.0 mmol/kg/24h, magnesium>±0.3 mmol/kg/24h, calcium>±0.5 mmol/kg/24h, phosphate>±0.5 mmol/kg/24h.

Objective was to determine the number of at least one clinically significant formulation change on unplanned and planned PN and associated factors (year with possible impact of the teaching program, unit, bodyweight [kg])

**Results:** A total of 306 PN prescription sequences were analysed (2015: 163, 2016:143): 252/306 (82%) were unplanned during the week-end, 54/306 (18%) planned. Unplanned PN were more prescribed in 2015 than in 2016 (57.1% vs 42.9%, \( p=0.004 \)), mainly for the neonatal and intensive care unit (81.4%) and for smaller patients compared to planned PN (median weight 2.4 kg [IQR 1.0 to 8.6] vs 11.7 [4.0 to 16.2], \( p< 0.001 \)).

Only 42/252 (16.6%) of unplanned PN had at least one clinically significant day-to-day formulation changes. A trend to more frequent clinically significant day-to-day formulation changes was observed for smaller patients (1.3 kg [IQR 0.9 to 3.7] vs 2.6 [1.0 to 9.6], \( p= 0.055 \)). More frequent significant changes in the formulation were for glucose (23/42 (54.8%)) and phosphate (16/42 (38 %)). No association of clinically significant changes was observed with the year or the unit.

**Conclusion:** About 75% of PN compounded during the week-end are unplanned and mainly for the neonatal and intensive care unit, where the most critical patients stay. Only 16.6% of the unplanned PN had at least one clinically significant formulation change justifying daily compounding in the pharmacy. The teaching program could impact in the difference of prescription between the 2 periods, however other cofounding factor may play a role and need further evaluation. Planned PN prescription for all patients during the week-end for non-intensive care unit will be economically evaluated as next step.

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Dietary lipid structure in early life does not program fat absorption in later life

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Objectives and study: Previously, we reported that feeding mice in early life with the experimental infant milk formula Nuturis® (eIMF) with a lipid structure more similar to human milk, i.e. with large (3-5 µm) lipid globules coated with milk phospholipids, resulted in a lower body weight and fat mass gain when challenged with a Western style diet later in life, compared to standard, control IMF (cIMF; Ped Res 72:362; 2012). The mechanism by which eIMF exerts this effect has remained unclear. It is known from literature that lipid uptake kinetics can be important, for example by determining the metabolic fate of absorbed lipids (storage versus oxidation). In this study, we tested the hypothesis that eIMF feeding in early life permanently affects the kinetics of fat absorption in mice.

Methods: We fed male, pair-housed C57BL/6JOlaHsd mice a rodent diet comprising cIMF or eIMF from postnatal day 16 to 42, followed by 3 weeks of a regular rodent diet (AIN-93G). At postnatal day 63, upon intraperitoneal injection of the lipoprotein lipase inhibitor poloxamer-407, fasting mice were administered a lipid bolus containing labeled fat (²H-oleic acid and tri-¹³C-olein) by gavage. We analyzed plasma lipids and appearance of ¹³C- and ²H-labeled lipids in blood samples taken at 0, 1, 2, 3 and 5 h after administration using gas chromatography-mass spectrometry. Values are given in means ± SD.

Results: In the eIMF and cIMF groups total plasma fatty acids/acyl chains increased similarly over the 5h course of the experiment: from 9±3 to 99±41 mM in cIMF and from 9±4 to 82±36 mM in eIMF, resulting in similar areas under the curve: 252±91 and 221±81 mM·h, respectively. Total plasma fatty acids/acyl chain increase rate between 1 and 3 h after gavage was 22±9 and 20±7 mM·h⁻¹ for cIMF and eIMF, respectively, indicating similar uptake rates from the intestine. The plasma appearances of ²H- and ¹³C-oleic acid were similar within and between groups. Interestingly, the plasma fat uptake kinetics between the two mice housed in pairs varied by at least a factor two in 10 out of 11 pairs, irrespective of being fed cIMF or eIMF in early life (p< 0.001).

Conclusion: Our data in mice indicate that exposure early in life to dietary fat in the form of larger lipid globules covered with milk phospholipids (Nuturis®) does not affect the kinetics of intestinal fat digestion and absorption later in life. The twofold difference found in fat uptake kinetics between pair-housed mice now warrants experiments to address whether this translates into different metabolic profiles and sensitivities later in life.

Disclosure of interest: The present study was funded by Nutricia Research. BJMvdH is employed by Nutricia Research. HJV is a consultant for Nutricia Research outside the submitted work, for which his institution is financially compensated.

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Factors influencing exclusive breastfeeding practices among Indian mothers

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Background and objective: Exclusive breastfeeding during first 6 months of life has been widely recognised and recommended as essential & beneficial for the child and also for the mother more so in a developing country like India. Yet practice of exclusive breastfeeding is low due to various reasons in India. National Family Health Survey - 3 (NFHS-3) has reported only 46.3% babies in India are exclusively breastfed during their first 6 months of life. Aim of this study is to determine the factors responsible for non-practice of exclusive breastfeeding.

Methods: This is a cross-sectional, observational self-administered questionnaire based survey conducted among mothers attending a paediatric clinic, in a metro city to understand the factors leading to non-practice of exclusive breast feeding.

Results: 339 mothers were interviewed for the clinical survey. More than 22% of children were never breastfed and only 47.34% of babies were exclusively breastfed in our survey. Study results indicate that Housewives have a higher probability of exclusive breastfeeding than working mothers (Odds ratio 1.26). Place of delivery also influences breastfeeding habit. Babies who are born in government hospitals have a higher chance of being exclusively breastfed for 6 months than both private corporate hospitals and private nursing homes (Odds ratio 1.96 and 1.09 respectively). Out of 339 mothers, we received history of mode of delivery of 174 mothers and surprisingly 86.78% has undergone caesarean section. Mothers undergone caesarean section, have a very high probability of never breastfeeding their child (Odds ratio 2.42 in comparison to normal delivery) and a lesser probability of exclusive breastfeeding for 6 months (Odds ratio 0.57). Premature babies have higher risk of never being breastfed than full term babies (Odds ratio 1.11) whereas full term babies have higher chance of exclusively breastfed than premature babies (Odds ratio 1.75). Financial status is also one of the important determinant and our study showed that mothers belonging to middle income group has higher probability of practicing exclusive breastfeeding than high income group (Odds ratio 1.36) whereas lower income group has a higher probability than middle income group (Odds ratio 1.32). Children who were born 10 years back and Children aged between 5-10 years has a higher probability of exclusively breastfed than children less than 5 years of age (Odds ratio 3.3 &2.78 respectively) which may indicate that women who became mother in last 5 years, are less motivated to continue exclusive breastfeeding for the first 6 months in comparison to earlier days.

Conclusion: The study showed that exclusive breastfeeding practices are dependent on Mother's socioeconomic status, place and mode of delivery, duration of pregnancy as well as age of the child. Further research is necessary to determine impact of each factor on breastfeeding habits and to delineate newer strategies to improve exclusive breastfeeding practices among Indian mothers.

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Longitudinal changes of mineral concentrations in preterm and term human milk from lactating Swiss women

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Objectives and Study: A correct supply of minerals to preterm infants is essential for normal growth and development. The objective of the study was to analyze and to compare the mineral content of human milk from mothers of preterm (28-32 weeks) and full term (< 37 weeks) infants at different stages of lactation. The comparison was performed at equivalent infant postpartum and postmenstrual ages, assessing additional factors like mode of delivery, twin vs. single delivery and infant gender.

Method: Human milk samples were collected from healthy mothers weekly for eight weeks and then biweekly up to four months for the preterm group (n=27). The term group (n=34) had weekly collections for eight weeks. The samples were analyzed for iron, zinc, selenium, copper, calcium, magnesium, phosphorus, potassium and sodium concentrations simultaneously by Inductively Coupled Plasma - Mass Spectrometry (ICP-MS). Iodine was determined separately by ICP-MS after an alkaline extraction.

Results: Mineral contents of both milks decreased over lactation without significant differences when compared at the same postpartum age. However, when milks from mother of preterm and full term infants where compared at equivalent postmenstrual age, significant differences were observed for zinc, copper, selenium sodium and iodine. Zinc and copper concentrations in term milk were significantly higher than in preterm milk from 38 to 48 week of postmenstrual age (p<0.000 and <0.002, respectively). Selenium and sodium concentrations was significantly different from week 38 to 44 (p<0.002 and p<0.01, respectively). Finally, iodine concentration in preterm milk was significantly lower at week 41 to 45 (p<LT; 0.03). No significant differences were found when comparing mineral concentrations by gender, mode of delivery or twin/single delivery.

Conclusion: The results provide comprehensive information on the temporal changes of ten minerals in preterm milk and could help to increase the accuracy of mineral fortification in preterm milk. The relevance of the observed differences to health, growth and development of preterm infants remains to be further investigated and confirmed by future intervention trials.

This trial was approved by the local Ethical Committee and registered at ClinicalTrials.gov under NCT02052245.

Disclosure of interest: All authors, except LB, JFT, CJFF are Nestlé employees.

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Comparison of fat absorption mechanisms in vivo between human milk and infant formula containing novel absorption enhancement technology

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Objectives and Study: Human milk (HM) lipids are better absorbed by infants compared to lipids delivered in infant formula (IF). Previously, our research showed that incorporation of a mixture of mono- and di-glycerides and phospholipids (MDG/PL) into IF improved lipophilic nutrient absorption compared to standard IF using the conscious lymph fistula rat model. Our primary goal was to understand whether the fat absorption mechanisms behind the absorption benefits of MDG/PL (novel absorption enhancement technology) are similar to those with HM, the gold standard for infant nutrition.

Method: We compared using a conscious lymph fistula rat model, the digestion and lymphatic transport of triglycerides (TG), phospholipids (PL), and fatty acids (FA) outputs of infant formulas versus fresh, non-pasteurized, non-frozen HM. Three groups of male adult Sprague Dawley rats (n= 6-12/group) were randomized to receive via the stomach infusion tube the same amount of lipid (3.5 g fat/100 mL) from either standard IF, IF containing MDG/PL or HM. Aliquots of lymph were taken at fasting and hourly for 6 hours for analysis of TG, PL, palmitic acids, arachidonic acids (ARA) and docosahexaenoic acid (DHA). Lymphatic output of number of chylomicrons (as determined by apolipoprotein (apo) B48 output) and their size distribution were also characterized in HM and IF variables.

Results: Similar to HM, gastric delivery of IF with MDG/PL over 6 hours significantly increased chylomicron secretion (apo B48 output- one chylomicron particle carries one apo B48; (3.0 fold; p&LT; 0.05)) and improves fat absorption (TG output; p&LT; 0.05) and lymphatic PL transport (p&LT; 0.05) versus standard IF. Significant increases in the absorption of palmitic acid, ARA and DHA were also observed with HM and IF containing MDG/PL as compared to standard IF. Chylomicron size distribution was similar between HM and all the other IF variables.

Conclusion: Fat absorption as indicated by lymphatic TG, PL, FA, and chylomicron outputs is shown to be more efficient from HM compared to standard IF. The incorporation of MDG/PL technology to IF improves fat absorption and chylomicron synthesis thus bringing the digestion and absorption of lipids within IF closer to HM.

Disclosure of interest: Mustafa Vurma and Stephen DeMichele are Abbott Nutrition employees.
Objectives and Study: The objectives of the study are: 1) to investigate the effect of high-dose maternal vitamin D supplementation of 6000 IU/day alone versus direct maternal supplementation of 600 IU/day plus infant supplementation of 400 IU/day on vitamin D status of exclusively breastfeeding mother-infant pairs in a population with endemic vitamin D deficiency, and 2) determine the effect of maternal vitamin D supplementation of 6000 IU/day on the vitamin D content of human milk in mothers at risk of vitamin D deficiency.

Method: In a control trial, we evaluated and compared the effect of six months supplementation of 6000IU/day vitamin D3 supplementation of mothers alone versus current recommendation of direct supplementation of 600IU/day of the mothers plus direct infant supplementation of 400IU/day on the vitamin D status of breastfeeding mothers and their infants. We monitored prospectively and recorded the vitamin D and calcium status of the two groups as well as the necessary safety parameters and reported the findings to a Data Safety Monitoring Board every quarter.

Results: Results and Conclusions. The characteristics and vitamin D status of exclusively breastfeeding mothers and infants in the two groups were similar at the start of the project. The average maternal vitamin D status measured as serum maternal 25-hydroxyvitaminD (25(OH)D) was 35.1nmol/L in mothers on 6000 IU/day and 35.7nmol/L in mothers on 600 IU/day vitamin D. Similarly, infants of mothers on high-dose supplementation had 25(OH)D of 31.9 versus 29.6 in infants of mothers on low dose supplementation. Mothers on 6000 IU/day vitamin D supplementation achieved a significantly higher average serum 25(OH)D of 98 nmol/L compared with 52 nmol/L in mothers on 600 IU/day vitamin D supplementation at the end of the 6 months supplementation. In addition, 96% of mothers in high-dose vitamin D supplementation group achieved serum 25(OH)D levels ≥50nmol/L considered as adequate compared with 52% in mothers on lower dose supplementation. The infants of mothers in 600IU/day group but had direct 400IU/day vitamin D supplementation had slightly higher increase in serum 25(OH)D level compared with infants of mothers in high-dose supplementation group (109 versus 92 nmol/L). However, infants in both groups achieved similar 25(OH)D levels ≥50 nmol/L considered to be adequate for bone health by IOM in the US. In addition, mothers on 6000 IU vitamin D3/day substantially improved breast milk vitamin D content which greatly benefited her nursing infant. There were no safety concerns in the mothers and infants to stop the progress of the study. Supplementation of breastfeeding mother with 6000 IU/day vitamin D3 alone is safe and deserve further exploration as an option to optimize mother’s vitamin D status and prevent vitamin D deficiency in her nursing infant.

Conclusion: Vitamin D deficiency is a public health problem in Arab countries including Qatar. This is the first study to show that vitamin D deficiency in mother-infant dyads with vitamin D supplementation of mother alone in a population with endemic vitamin D deficiency.

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**NUTRITION - Neonatal and infant nutrition**

N-P-132

**mRNA expression of TLR2 and TLR4 in healthy infants according to age**

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**Objective ad Study:** Toll-like receptors (TLRs) are class of protein and play a role in the innate immune system since they are expressed on the membranes leukocytes, macrophages and non immune cells.

Toll-like receptors are activated by different ligands, which are located on different types of organisms or structures (such as gut bacteria).

TLRs 2 and 4 are extracellular TLRs that are recognized as innate immune receptors that bind a wide range of endogenous ligands and gut microbes.

TLRs are potentially are indicators of several conditions by which inflammation is regulated by interactions between microbiota and the host.

Scanty data are available on the expression of TLRs in postnatal healthy infants.

**Methods:** Aim of this study was to investigate the expression of the mRNAs of TLR2 and TLR4 in blood samples obtained from healthy full-term infants using real-time PCR. We enrolled healthy children during outpatient control at the Department of Pediatrics (Regina Margherita Children Hospital, Turin, Italy), and parents gave written informed consent.

The research protocol was approved by the local ethics committee (Comitato Interaziendale AA.SS.OO. O.I.R.M./S. Anna-Ordine Mauriziano di Torino).

Venous blood samples were collected at 8 a.m. during routine blood exams.

**Statistical analysis** All data are reported as relative quantities. Data samples were analysed with the Mann-Whitney test. All tests were two-tailed and considered significant at values of p<0.05.

**Results:** We analysed the mRNA expression levels of TLRs in 75 healthy term children divided according to age. The median expression level of TLR2 was 1.52 ±1.21 Arbitrary Units (AU) (n=26) in infants younger than 3 months old, 0.65 ± 0.73 AU (n=24) in infants between 3 and 12 months old, and 0.05 ± 0.02 AU (n= 25) in infants between 12 and 18 months old.

The median expression level of TLR4 was 1.29 ±0.81 AU (n=26) in infants younger than 3 months old, 0.77 ± 0.56 AU (n=24) in infants between 3 and 12 months old, and 0.45 ± 0.29 AU (n= 25) in infants between 12 and 18 months old.

We found differences in the mRNA expression values of TLR2 and TLR4 between infants aged 0-3 and 3-12 months old and those aged more than 1 year old (p&LT; 0.0001 and p&LT; 0.0001, respectively).

**Conclusion:** The present study attempt to characterise how TLR2 and TLR4 expression changes with age in healthy infants, we observed that their expression are significantly higher during the suckling period and then decreased once the infants reached 1 year old (p&LT; 0.001). Further investigations are needed if these findings are related to gut microbial colonization.
Feeding difficulties in infants hospitalized in a NICU: an observational study.

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Objective and Study: Most infant feeding problems such as feeding difficulties occur in early infancy and involve preterm infants. Premature birth is not a direct cause of long-term feeding disorders, but with decreasing gestational age comes an increase in morbidities and illnesses, such as bronchopulmonary dysplasia, necrotizing enterocolitis, neurological abnormalities. Congenital malformation such as oropharyngeal abnormality, atresia esophageal, or hernia diaphragm can determine feeding difficulties. Little is known on feeding outcomes during hospitalization of these subjects.

Objectives: This study is an observational study aimed to collect data on newborn and infants recovered in a NICU with regard feeding difficulties using a standardized questionnaire Behavioral Pediatric Feeding Assessment Scale (BPFAS) by parents and by Nurse.

Methods: All newborns admitted at our Unit from September 2016 to October 2017 were enrolled. Demographic and anthropometric data as well as nutrition referral status were documented during the clinic visit. Parents or Nurses of clinic patients, who gave written consent, received the BPFAS and interviewed with assistance by a pediatrician. Dysphagia,odynophagia,unco-operative swallowing, crying during feeding, vomiting and diarrhea, eczema, failure to thrive, and developmental disability, were used as signs to diagnosed feeding difficulties. Mean BPFAS scores were compared by survey administration method and nutrition referral status using the t-test.

Results: A total of 248 newborns were admitted at our NICU, and 170 subjects agreed to participate and were enrolled. Among these newborns, the prevalence of preterm birth was 31%, of perinatal morbidity was 54%, and of neonatal mortality was 3. Feeding difficulties was reported by 38 % of parents and by 53 % of health care professionals (nurses) using scale Behavioral Pediatric Feeding (p&LT; 0.05) Nutritional support: Total parenteral nutrition was employed in 27 % of patients, tube feeding needs in hospital in 25% of patients, 3% of infants required Percutaneous endoscopic gastrostomy tube insertion to maintain proper nutritional status at home. Swallowing difficulties were observed in 21% of patients, Congenital malformation which required surgical corrections in 17%, of which 6% were oropharyngeal abnormality.

Conclusions: This study showed that infants hospitalized in a NICU had a higher risk of feeding difficulties mainly in hospital and sometime at home. However, determining the prevalence of feeding problems may be complicated since there is no universally accepted definition or classification system. Multidisciplinary evaluation of feeding assessment surveys in these patients appear to be necessary. Our data showed that there was a difference in the BPFAS total score obtained when administered at the family or at the nurses. Larger prospective studies may be useful to assess this tool and to evaluate the risk factors for long term feeding difficulties, such as PEG at home.
Extrauterine growth retardation (EUGR) on very low birth weight infants after CSPEN guidelines for nutrition support in NICU

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Objectives and Study: Extrauterine growth retardation (EUGR) in very low birth weight (VLBW) infants indicates that the nutrient requirements have not been adequately met intrauterine growth. The aim of this study is to describe the growth and nutritional practices in VLBW infants during NICU after CSPEN guidelines for nutrition support in neonates (2013), and compare the incidences of EUGR at discharge.

Method: We retrospectively studied 227 VLBW infants (115 boys and 112 girls) from Shanghai Children's Medical Center in Shanghai from January 1, 2014 to December 31, 2016. When admission, these infants were grouped small gestation age (SGA) and appropriate gestation age (AGA). Growth retardation was defined according to weight or head circumference (HC) ≤ 10th percentile of the growth value expected based on estimated postmenstrual age by Fenton Preterm Growth Chart (2003). Nutritional practices were analyzed between AGA and SGA.

Results: From the growth during the first 21 days, there is no significance of Day on the lowest weight between SGA and AGA (4 vs 4, p > 0.05). When Day to regain birth weight, it is not significant between the two groups (41 vs 10, p > 0.05). At discharge, the incidences of EUGR are 65.2% by weight and 39.6% by HC. SGA had a significantly higher rate of EUGR compared with AGA (97.8% vs 55.8% by weigh, p < 0.05; 69.7% vs 32.0% by HC, p < 0.05). By brief parenteral nutrition analysis, there were no significances of energy, glucose, amino acid and lipid. There is significance of PN duration and the use of PICC between AGA and SGA (31.4 VS 19.9, p < 0.05; 47.5% VS 32.6%, p < 0.05). At the end of PN, there is significance of calories percent in EN between AGA and SGA (67.5% VS 61.7%, p < 0.05). Meanwhile, Days to reach full feeds shows a significance between the two groups (23.6 VS 15.0, p < 0.05).

Conclusion: The incidence of EUGR might be decreased after CSPEN guidelines for nutrition support in neonates (2013). But there is higher incidence of EUGR in AGA group, and SGA group still shows growth retardation. It is crucial to determine the optimal enteral nutrition for VLBW infants.

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Taste experiences and food exposure in weaning age: a qualitative exploration of maternal perceptions, attitudes and practices

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Objectives and Study: Weaning marks the transition from a milk-only diet to the consumption of solid foods. It is a time period where nutrition holds an undeniable importance and taste experiences have a long-lasting effect on food preferences. The circumstances under which parental feeding practices are formed are yet to be understood; doing so will help us target any problematic behaviours and modify them. This study aims to investigate mothers' perceptions, attitudes and practices in relation to their babies' food likes and dislikes, food exposure and diet diversity during weaning.

Method: We recruited 37 mothers of healthy infants 3-14mo with no previous history of allergies or food-related disorders. We conducted 8 semi-structured focus group discussions which were transcribed and analysed thematically.

Results: Five main themes emerged during the analysis:
1) how babies form their taste preferences,
2) strategies to facilitate acquisition of food preferences,
3) communicating food dislike following food exposure,
4) perceived importance of food variety in weaning,
5) perceived importance of feeding environment.

Conclusion: Mothers were aware of their role in shaping their babies' food preferences and used strategies such as modelling behaviour and repeated food exposure to influence them. Head and body movements were perceived as cues for food aversion, but not facial expressions. The importance of a diverse diet in infancy was well acknowledged, whereas knowledge gaps exist in relation to its definition and value in the weaning context. Feeding practices did not comply with recommendations advising on a peaceful and enjoyable feeding environment. Our findings provide an insight into the weaning process from a mother's perspective that can be used to guide the design of educational interventions in this area.

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NUTRITION - Neonatal and infant nutrition

N-P-136

Improving the use of mother's own milk for very low birth weight infants in the neonatal intensive care unit

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Objectives and Study: Breastfeeding rates in Ireland are significantly lower than counterpart countries. Breastmilk provides protection for premature infants against key causes of morbidity and mortality including sepsis, necrotising enterocolitis and retinopathy of prematurity. This project aimed to improve enteral nutrition for premature infants by advocating the early and sustained use of mothers own milk. The WHO Baby Friendly Hospital Initiative standards were consulted which promotes exclusive breastfeeding for all infants. In addition hospital guidelines advise for all infants to have received their mother's milk by 2-6 hours of life, and where this is not available, to receive donor milk by 48 hours in those weighing less than 1kg.

Method: A Quality Improvement (QI) project was designed looking at the strengths and weaknesses within the organisation and the drivers for change. Quantitative and qualitative measures were evaluated using Statistical Process Control tools and the Kirkpatrick Framework. Audit was performed as part of multiple Plan Do Study Act (PDSA) cycles. This involved an initial retrospective chart review of 20 infants less than 32 weeks gestation and weighing less than 1.5kg admitted to the Neonatal Intensive Care Unit between June and August 2016. Questionnaires were administered to mothers and staff. Education sessions were delivered including a staff information booklet and a revised feeding chart was introduced. Lactation support hours were increased. Bimonthly re-auditing and feedback of data promoted ongoing change. Re-auditing was performed prospectively on a bimonthly basis as part of multiple PDSA cycles. Results of key performance indicators were presented using run charts to show change over time.

Results: A baseline audit of 20 infants born with mean gestational age 28 (SD, 1.6) weeks and mean birth weight 970 (SD, 218) g found that the average time to first feed was 19 hours, while 5 (25%) infants received their mother's milk exclusively in the first 7 days of life. Repeat chart reviews of 24 infants with mean gestational age 27.4 (SD, 1.8) weeks and mean birth weight 972 (SD, 266) g post intervention born between November 2016 and March 2017 showed that, 23 (95.8%) received their mothers own milk, 16 (66.7%) exclusively. In addition 12 (50%) received their first feed within the target 6 hours of birth. The incidence of feed intolerance fell from 35% to 29.2% post intervention.

Conclusion: Infant nutrition outcomes were improved through education and increased support to mothers and staff. Sustainability was achieved through combined multidisciplinary efforts and ongoing feedback of data.
Comparison of continuous versus intermittent bolus feeding in preterm infants ≤ 32 weeks and ≤1250g

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Objectives and Study: Current evidence is equipoised neither favouring continuous feeding nor intermittent feeding as a feeding strategy to improve tolerance to full enteral feeds in very preterm infants. In addition, intermittent feeding by infusion has not been studied in clinical trials. Eligible infants were randomly assigned to three groups− continuous infusion (CI), intermittent bolus by infusion (IBI) and intermittent bolus by gravity (IBG). Primary objective was to compare in the three groups -time taken to reach full feeds and secondary objectives were episodes of feed intolerance, time to regain birth weight, proportion of infants who developed necrotizing enterocolitis and sepsis, growth velocity at stoppage of intervention and at discharge, duration of hospital stay, morbidities during hospital stay and all-cause mortality.

Method: Randomized Controlled trial

Results: Of 168 eligible infants, 129 infants were enrolled. Ninety seven infants could reach the primary outcome. The mean (SD) gestation of infants in CI, IBI and IBG were 28.3 (2.3) wk, 28.5 (1.9) wk and 28.6 (1.8) wk respectively. There was no difference in time to reach full feeds in infants enrolled in CI, IBI and IBG, [median (IQR) 16 (12-23.2), 16 (14.5-26) and 15 (11.5-17.5) days, respectively, p=0.70]. Proportion of infants who developed feed intolerance in CI, IBI and IBG were similar, [17 (48.6%), 17 (53.1%) and 19 (65.5%) respectively, p=0.38] (table 1). In addition, there was no difference in other secondary outcomes including growth characteristics.

Conclusion: In preterm infants ≤ 32wk of gestation and birth weight ≤ 1250g, time to reach full enteral feeds is similar in all three feeding methods.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Group A CI (n=35)</th>
<th>Group B IBI (n=33)</th>
<th>Group C IBG (n=29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full feeds (days) *</td>
<td>16(12-23.2)</td>
<td>16(14.5-26)</td>
<td>15(11.5-17.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>100ml/kg/day (days)*</td>
<td>12 (8-15.2)</td>
<td>12 (9.5-17)</td>
<td>11 (7.5-14.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>TBW (days) €</td>
<td>9.8 (5.5)</td>
<td>10.7 (5.5)</td>
<td>10.0 (3.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Duration of PN*</td>
<td>11 (8-15.5)</td>
<td>14 (10.5-15.5)</td>
<td>11 (7.5-13.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>DOI day*</td>
<td>36 (28-54)</td>
<td>44 (26-59)</td>
<td>34 (24-53)</td>
<td>0.55</td>
</tr>
<tr>
<td>Feed Intolerance n (%)</td>
<td>17 (48.6%)</td>
<td>17 (53.1%)</td>
<td>56 (18-102) 62.1</td>
<td>0.38</td>
</tr>
<tr>
<td>NPO hours*</td>
<td>50 (18-102.5)</td>
<td>56 (18-102)</td>
<td>42 (17-115)</td>
<td>0.87</td>
</tr>
<tr>
<td>EHM (%)</td>
<td>63.3</td>
<td>62.1</td>
<td>66.1</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Median (IQR), € Mean (SD), TBW-time to regain birth weight, PN-Parenteral nutrition, NPO-Nil per os, DOI-duration of intervention, EHM-Expressed Human Milk.

[Table 1: Outcomes in infants who reached full feed]
**Objectives and Study:** Inclusion of bovine-derived milk fat globule membrane (MFGM) or MFGM components in infant formulas may support healthy brain development in infants and young children. Recent expert recommendations also support use of infant formulas with adjusted protein, arachidonic acid (ARA), and iron. The objective of this study was to evaluate growth, tolerance, and iron status in healthy infants who received investigational cow’s milk-based formula with whey protein-lipid concentrate (5 g/L, source of MFGM) and adjustments in protein, ARA, and iron.

**Method:** In this multi-center, double-blind, controlled, parallel-group, prospective study, infants were randomized to receive one of two formulas through 365 days of age (each with docosahexanoic acid, 17 mg/100 kcal): 1) Control (n=191): marketed, routine cow’s milk-based infant formula (per 100 kcal: ARA, 34 mg; protein, 2.1 g; iron, 1.8 mg) or 2) INV-MFGM (n=182): investigational cow’s milk-based formula (per 100 kcal: protein 1.9 g; ARA, 25 mg; iron, 1.2 mg; whey protein-lipid concentrate, 5 g/L). The primary outcome was growth rate from 14 to 120 days. Growth rates through 120 days and achieved anthropometrics through 365 days of age were analyzed by gender using ANOVA. Parental 24-hour recall of formula intake, stool characteristics, fussiness, and gassiness were also evaluated. A blood sample was collected at 365 days of age and blood markers, including hemoglobin (Hb) and hematocrit (Hct), were evaluated to assess iron status.

**Results:** No significant group differences were detected for weight, length, or head circumference growth rates by gender for any age range from 14 to 120 days of age. No significant group differences were detected for mean achieved anthropometrics by gender at any time point assessed, with the exception of mean achieved weight in female infants at day 365. Group mean achieved weights by gender plotted within the 25th and 75th reference percentiles of the WHO growth standard at all study time points assessed with the exception of female infants in the Control group (remained between the 25th and 75th percentiles of growth through day 180 and tracked near the 75th percentile through day 365). No group differences in overall study discontinuation or study formula discontinuation were detected. Few group differences were detected in parental-reported fussiness, gassiness, or stool frequency or consistency during the study period. No significant group differences were detected in Hb, Hct, or the risk of anemia.

**Conclusion:** In healthy infants, MFGM and adjustments in protein (1.9 g/100 kcal), ARA (25 mg/100 kcal), and iron (1.2 mg/100 kcal) in a routine cow’s milk-based infant formula were well-tolerated, associated with normal growth, and supported normal iron status throughout the first year of life.
**Objectives and Study:** Market data show high sales of commercial complementary foods (CCF) in western European countries. However, there are few research studies on how CCF affect dietary intakes of infants and young children in Europe and which demographic characteristics predict their use. We investigated overall intakes and predictors of commercial complementary food use (CCF) in a large cohort of European infants over the first two years of life.

**Method:** Dietary data was drawn using 3-day dietary recalls from the European Childhood Obesity Project (CHOP) cohort. CHOP is a multicenter intervention trial in Germany, Belgium, Italy, Poland and Spain that tested the effect of varying levels of protein in infant formula on the risk for childhood obesity.

**Results:** CCF use was common with a range of 25.60% - 94.4% of the cohort reporting exposure between 4 and 24 months of age. Exposure to CCF was highest between 7 and 12 months of age (≥92.7%). Sweetened CCF use was highest in Spain, Italy, Poland and in formula-fed infants.

**Conclusion:** European nutrition directives should take into account the significant contribution of commercial complementary foods to European infant diets. More studies on the quality of commercial complementary foods in Europe are warranted.
Disclosure of interest: The Ludwig-Maximilians-Universität München and its employees BK and VG have received support for scientific and educational activities by a variety of nutritional companies, predominantly as part of publicly funded research projects with support of the European Commission or German governmental research support. None of this support has influenced the writing and conclusions of this manuscript.
Can we define standard concentrations of oligosaccharides in human milk?

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Objectives and Study: Human milk oligosaccharides (HMOS) consist of several hundreds of complex built glycans. This diverse mixture has been described to have numerous beneficial functions in infants, including a prebiotic effect and furthermore direct immune effects and protection against infection. The aim of this literature review was to identify the main factors that affect the concentrations of HMOS and to determine whether it is possible to indicate representative standard concentrations.

Method: A comprehensive literature search (until August 2015) on HMOS has been performed in 6 electronic databases. The application of strict inclusion criteria (milk samples from healthy mothers, documented duration of pregnancy and of lactation, defined secretor status, mean values or single values with \( n \geq 2 \), publication in peer-reviewed journals) resulted in 21 studies selected. The screening of very recent articles (until November 2017) yielded two further studies meeting the above-mentioned inclusion criteria.

Results: Mean concentrations, including confidence limits (CL), of 33 neutral and acidic oligosaccharides reported could be calculated (Thurl et al. 2017). Concentrations of HMOS showed variations that are dependent on both the secretor type of the mother and the lactation period as examined by analyses of variance. In addition, large interlaboratory variations in the data were observed. Recent studies indicated influence of secretor status, lactation period, geographical location and possibly ethnicity on HMOS concentrations (Sprenger et al. 2017, McGuire et al. 2017). Mean concentrations of major HMOS from secretor mothers reported in the 3 studies mentioned above are shown in the Table.

<table>
<thead>
<tr>
<th>HMOS</th>
<th>Thurl et al. Means (g/L)</th>
<th>95% CL (g/L)</th>
<th>McGuire et al. Means (g/L)</th>
<th>Sprenger et al. Means (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2'-FL</td>
<td>2.74</td>
<td>2.43 - 3.04</td>
<td>2.46</td>
<td>1.77</td>
</tr>
<tr>
<td>3-FL</td>
<td>0.44</td>
<td>0.31 - 0.58</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>LNT</td>
<td>0.79</td>
<td>0.59 - 0.98</td>
<td>0.98</td>
<td>0.67</td>
</tr>
<tr>
<td>LNnT</td>
<td>0.74</td>
<td>0.36 - 1.12</td>
<td>0.57</td>
<td>0.18</td>
</tr>
<tr>
<td>LNFP I</td>
<td>1.31</td>
<td>1.08 - 1.53</td>
<td>1.24</td>
<td></td>
</tr>
<tr>
<td>LNFP II</td>
<td>0.28</td>
<td>0.21 - 0.34</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>3'-SL</td>
<td>0.19</td>
<td>0.14 - 0.24</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td>6'-SL</td>
<td>0.64</td>
<td>0.38 - 0.91</td>
<td>0.30</td>
<td>0.32</td>
</tr>
</tbody>
</table>

[Mean concentrations of major HMOS from secretors]

The mean values reported in the studies of Sprenger et al. (34 women at 30 - 120 days postpartum) and McGuire et al. (316 women at 49 - 73 days postpartum) are not all within the confidence limits that have been calculated in the review article of Thurl et al. (51 - 353 women at 1 -120 days postpartum). Particularly high deviations can be detected with the HMOS 3-FL and LNFP II, respectively.

Conclusion: Data on the concentrations of HMOS are a prerequisite for understanding the biological functions and complexity and should help guide further developments in infant nutrition. Due to the large variability of HMOS it is necessary for future studies to exactly report the relevant parameters of milk sampling, i.e. health conditions of mothers and infants, gestational age, Lewis blood groups of the mothers (at least the secretor status), ethnicity, geography, time postpartum, sampling techniques. The large data variations between the studies also could be due to the influence of the quantification
method. Therefore, worldwide interlaboratory analyses of identical milk samples are required to identify the most reliable methods of determining concentrations of HMOS.

References:

Disclosure of interest: Bernd Stahl is an employee of Danone.

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Neonatal cholesterol provided by breast milk and the gap in nutrition support solutions

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Objectives and Study: Neonatal parenteral nutrition (PN) and enteral nutrition (EN) research has recently focused on improving fatty acid composition without attention to cholesterol. Infants on exclusive PN have been shown to have a different cholesterol-lipid protein profile in their blood as compared to healthy infants because of the phytosterol composition. In addition, it is well known that developmental scores are decreased in infants on long term PN as well as infants with illnesses requiring long term EN. Cholesterol is involved in vitamin, bile acid, lipoprotein, and hormone synthesis in growing infants and is involved in brain development and myelination. Measurement of human breast milk cholesterol has consisted of small individual samples, however these data do demonstrate that human milk contains more cholesterol than infant EN and PN formulas. Re-examining a large global cohort is the first step in targeting cholesterol in nutrition support solutions.

Method: In a large (n=360 mothers; 120 mothers per site) prospective, longitudinal, Global Exploration of Human Milk (GEHM) cohort study we examined the cholesterol concentrations of human milk from three distinct urban populations in Shanghai, China, Mexico City, Mexico and Cincinnati, USA. Enrollment was limited to healthy mothers of term, singleton infants. Sample collection was standardized as a full breast expression during a 4 hour window (9am-1pm) at 4 weeks of infant age. Milk was saponified in alcoholic KOH, sterol extracted, and mass of cholesterol measured by gas liquid chromatography GC using stigmastanol as an internal standard.

Results: Breast milk cholesterol concentration (mg/100mL) differed significantly between all sites with the highest levels in Cincinnati followed by Mexico City and Shanghai (mean ± SD): 14.5 ± 5.1, 11.1 ± 6.4, 10.2 ± 3.8, respectively (P&LT; 0.001). Among the sample as a whole, breast milk cholesterol levels were significantly different between BMI classes, with higher classes having higher cholesterol levels (P=0.001). Both pre-pregnancy BMI and delivery BMI were positively correlated with breast milk cholesterol levels (P &LT; 0.001 R^2 = 0.04, P &LT; 0.001 R^2 = 0.03). The median concentration of cholesterol from normal weight mothers (BMI 18.5-24.9) in the large cohort was 10.75 mg/100mL, which is substantially higher than EN range reported (1.7-3.8 mg/100 mL) and PN (0 mg/100mL) formulas. In fact, a cumulative deficit of about 1500 mg cholesterol in a EN-fed or PN-fed infant could be realized as compared to a healthy nursing infant over four weeks.

Conclusion: Human milk cholesterol levels, provided largely via milk fat globule membrane (MFGM) are significantly greater than that provided by EN or PN which results in a paucity of intake in the non-nursing infant. New dairy technologies could provide MFGM cholesterol to narrow this gap.

Disclosure of interest: AS and CV; employees of Mead Johnson Nutrition

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Highly efficient fat absorption with improved uptake of palmitate and calcium from an infant milk formula concept comprising large phospholipid-coated fat globules and 48% milk fat

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Objectives and study: Fat and calcium in infant formulae (IF) are important for adequate growth and (bone) development. Fat and calcium absorption from human milk (HM) and IF are highly efficient, and may be related to fat quality. HM fat globules are on average 4 µm in diameter and surrounded by a biological membrane. The new concept IF (Nuturis®) contains large, 3-5 µm, fat globules coated with milk phospholipids. Fat structure in this concept IF is more similar to HM than current IF containing small (0.5 µm) uncoated fat globules1. As previously reported, the randomized, multi-country, double-blinded, prospective, controlled clinical trial MERCURIUS demonstrated this new concept IF to be well tolerated and to support adequate growth2. The concept IF was also shown to have a stool-softening effect, closer to HM3. Aim of the current study was to test the effect of this new concept IF on fat and calcium absorption by stool content analysis.

Methods: Full formula-fed infants were enrolled up to 35 days of age and assigned to receive until 4 months of age either Control IF: current IF containing a 100% vegetal oil blend, or Test IF: the new IF concept comprising Nuturis® and a fat blend with 48% milk fat, replacing palm oil, resulting in ~6 %FA β-palmitate (vs. ~2 %FA in Control IF). Apart from fat quality, formula compositions were identical. The reference group consisted of infants exclusively breastfed until at least 3 months of age. Stool samples were collected at baseline (≤ 5 days), at 3 months (i.e. during IF intervention) and at 12 months of age (post-intervention). Differences in stool parameters between IF groups were evaluated at each sampling point using Wilcoxon’s rank-sum test.

Results: Faecal fatty acid (FA) content decreased from 9 w% at baseline to 1 w% at 12 months in both IF groups. At 3 months, i.e. during exclusive IF feeding, the Test group showed significantly lower faecal FA levels than Control (p<0.001); levels in both groups were similar at baseline and 12 months. Likewise, faecal palmitate (C16:0) content was similar between IF groups at baseline and 12 months, but was significantly lower in the Test group compared to Control at 3 months: 42 %FA vs. 65 %FA, respectively (p<0.001). Also, at 3 months calcium in stools was significantly lower in the Test group than Control (p=0.014), but did not differ at baseline or 12 months. Faecal FA, palmitate and calcium levels in the breastfed reference group were below (baseline, 3 months) or comparable (12 months) to the levels in both IF groups.

Conclusions: Faecal FA content was low in all groups and decreased with age, showing optimal fat absorption and maturation over time. The fat moiety in Test IF comprising Nuturis® and 48% milk fat shows a highly efficient, and closer to HM, total fat absorption compared to a standard Control IF. The data confirm the notion that the presence of β-palmitate can improve palmitate and calcium absorption, which may be instrumental to the previously observed stool-softening effect.

Disclosure of interest: M. Kalenga, O.F. Norbrujs, Y. Vandenplas, S.N.J. Jespers, A.C. de Mol, P.C. Khoo, S. Peeters, R.H.T van Beek, A.C.S. Hokken-Koelega, and members of Mercurius Study group declare a conflict with study funding. B.J.M. van de Heijning, S. Schoen, D. Acton, and E.M van der Beek are employees of Nutricia Research.

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Administration of infant formula supplemented with Pre-digested Fat (PDF) reduces the severity of Necrotizing Enterocolitis (NEC) and NEC-induced Lung Injury in mice

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³Johns Hopkins University and Johns Hopkins Children's Center, Baltimore, United States
⁴Children's Hospital of Pittsburgh, Pittsburgh, United States

Objectives and Study: Necrotizing enterocolitis (NEC) is a devastating disease that is typically aggravated after formula administration, suggesting that dietary components may influence disease pathogenesis. Fats are major components of infant formula, whose digestion requires pancreatic lipases which may be deficient in premature neonates. We hypothesize that the severity of NEC develops in part from the accumulation of incompletely digested fat within the intestinal lumen leading to oxidative stress, inflammation, and enterocyte toxicity, and that administration of a novel formula containing PDF can reduce the severity of NEC and NEC-induced lung injury, and sought to determine the mechanisms involved.

Method: We tested this hypothesis by inducing NEC in C57BL/6 mouse pups (7-8 days old) using either standard infant formula or formula containing either pre-digested or very low fat, along with hypoxia and bacterial challenge cultured from the stool of NEC infants. The outcome measures were pertaining to lipid oxidation, inflammation, and maturation of both gut and lung.

Results: The administration of the formula containing PDF significantly reduced NEC severity as well as NEC-induced lung injury. In seeking the mechanisms involved, the expression of carboxyl-ester lipase in the intestine was significantly lower in immature compared to mature pups. Standard formula administration resulted in the accumulation of intra-enterocyte triglycerides and generation of reactive oxygen species (ROS) that caused intestinal inflammation which were reversed in pups fed formula containing PDF or formula containing very low fat. Supplementation of standard formula with the ROS scavenger N-acetylcysteine (NAC) resulted in a reduction in intestinal inflammation and NEC severity. Moreover, exposure of mice to formula that contained PDF showed significantly reduced NEC-induced lung injury, as revealed by a reduction in histological changes to the lung and reduced expression of pro-inflammatory gene expression.

Conclusion: Taken together, these findings suggest that formula containing PDF can offer novel preventive approaches against NEC and NEC-induced lung injury when breast milk is not available.

Disclosure of interest: Mustafa Vurma and Tapas Das are Abbott Nutrition employees. This research was funded in part by a Sponsored Research Grant from Abbott Nutrition.
Role of insulin-like growth factor-I in early growth of preterm very low birth weight infants with different protein content

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Objectives and Study: Protein is the predominant component for developing tissue in preterm very low birth weight infants (VLBWIs). Insulin-like growth factor-I (IGF-I) stimulates cell growth and protein synthesis. The aim of the study was to evaluate early preterm VLBWIs growth with different protein content and to explore the relationship between early preterm VLBWIs’ growth and serum IGF-I levels.

Methods: Clinical data of 51 appropriate for gestational age preterm VLBWIs were analysed. According to different content of protein intake during the first 2 weeks, they were divided into high protein group and common protein group. The content of protein intake in the high protein group were at least 3g/kg/d while in the common protein group were less than 3g/kg/d during the first 2 weeks. The body weight at the 1st and 2nd week of the two groups were compared. The serum IGF-I levels of the two groups were analyzed at postnatal 1st week and 2nd week and were also compared.

Results: The high protein group (n=28) and common protein group (n=23) were comparable for gestational age (29.6±2.2 weeks vs. 29.5±2.3 weeks, P>0.05), birth weight (1265.04±165.24 g vs. 1250.11±169.38 g, P>0.05). The body weight at 1st week were significantly higher in the high protein group (1261.34±134.50 g) compared with the common protein group (1218.26±162.34 g) (P&LT; 0.05). The body weight at 2nd week were significantly higher in the high protein group (1494.51±184.84 g) compared with the common protein group (1366.64±193.13 g) (P&LT; 0.05). The serum IGF-I levels of at 1st week and 2nd week were significantly higher in the high protein group (w1: 32.43 ±9.25 ng/ml, w2: 53.32 ±12.26 ng/ml) compared with the common protein group (w1: 25.52 ±8.62 ng/ml, w2: 38.39 ±8.44 ng/ml) (P&LT; 0.05).

Conclusion: IGF-I involved in the regulation of early preterm VLBWIs’ growth. They should be given aggressive nutrition early for optimal growth.

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Simultaneous measurement of fat-soluble vitamins by liquid-chromatography coupled with tandem mass spectrometry in dried blood spots

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Objectives and Study: Investigation the effect of fat-soluble vitamins with neonatal development and disease are receiving more and more attention. DBS are often used for analysis of infant blood. However, simultaneous measurement of fat soluble vitamins, including 25-hydroxyvitamin D3 (25(OH)D3), 3-epi-25(OH)D3, 25(OH)D2, retinol, and α-tocopherol in dried blood spots is limited.

Method: Fat soluble vitamins were simultaneously quantified by UPLC-MS/MS. Antioxidant was used to increase the stability of vitamins under -20°C. Vitamin depleted whole blood was used to create calibration curves.

Results: After vitamins extraction, phospholipids depletion, and partial derivatization, 25(OH)D3, 3-epi-25(OH)D3, 25(OH)D2, retinol, and α-tocopherol were determined by UPLC-MS/MS on a triple quadrupole mass spectrometer. With the artificial vitamin depleted whole blood, the limits of quantification for 25(OH)D3, 3-epi-25(OH)D3, 25(OH)D2, retinol, and α-tocopherol were 5nM, 2nM, 2nM, 0.5µM, and 5µM, respectively. Furthermore, all these vitamins were stable for more than two month under -20°C with antioxidant protection. This method was subsequently applied for the measurement of fat soluble vitamin levels in newborn infants.

Conclusion: The developed method enabled long-term storage of fat soluble vitamins and specific quantification of these vitamins in DBS, which showed good utility in neonatal clinical studies.
The effects of maternal nutrition on lipid and microbial composition of breast milk and on infant gut microbiota

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Objectives and Study: Previous studies showed that both maternal and environmental factors have a strong influence on the composition of breast milk, in particular fatty acids. Recent studies have shown that breast milk also contains bacterial communities that may affect the health of the newborn. Yet how bacterial communities in breast milk are affected by maternal nutrition and the impact these bacteria have on the infant gut microbiota is unclear. The aim of the study was to investigate whether and how maternal nutrition and lipid composition in breast milk affects milk and gut bacterial content.

Methods: We collected human milk samples, from 22 healthy women, at 3-time points (first week of birth, 1 month and 3 months). In addition, the mothers filled food frequency questionnaires. We correlated nutritional variation in the mother diet and milk fatty acids composition, to milk bacterial composition. In addition, offspring fecal samples were collected for bacterial analysis.

Results: In all milk samples the most abundant genera were Streptococcus, while in the infant fecal samples the most abundant families were Bifidobacteriaceae and Enterobacteriaceae. In addition, five bacterial taxa were identified in all the milk samples that were collected. In the correlations with the mother’s nutrition, we found that high consumption of unsaturated fatty acids correlated with a lower concentration (polyunsaturated: \( r = -0.734, p = 0, q = 0 \), monounsaturated: \( r = -0.668, p = 0.001, q = 0.0922 \)) of Streptococcus in the milk. This correlation was also found with high B12 (\( r = -0.695, p = 0, q = 0 \)) and folic acid (\( r = -0.669, p = 0.001, q = 0.098 \)) consumption. In the context of milk’s fatty acids, there was a strong negative correlation between oleic acid and Streptococcus abundance in milk (\( r = -0.796, p = 0, q = 0 \)) and a strong positive correlation between MCFAs and staphylococcus abundance in milk. We did not find any association between fatty acids in the breast milk or bacterial milk composition and the baby’s intestinal microbiome.

Conclusion: These results shed light on the mother’s nutritional ability to influence mainly the composition of her milk bacteria, although clearly there is much room for future research.

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**Zinc status in infants and children with cholestatic liver diseases and its effect on growth**

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**Objectives and Study:** Zinc deficiency in children with cholestatic liver diseases could affect growth and immunity. Zinc supplementation is one of strategies to prevent the consequences of zinc deficiency in children. We aimed to study the effect of zinc supplementation on the growth of children suffering from cholestatic liver disease.

**Method:** Fifty-five infants and children (0.5-10 years) with cholestatic liver diseases enrolled from pediatrics hepatology clinic, Cairo university hospital, Egypt: 27 post Kasai, 7 with Alagille syndrome, and 21 with progressive familial intrahepatic cholestasis. Serum zinc level, insulin like growth factor 1 (IGF1) and anthropometric measurements [weight, weight percentile, weight Z score, height (length) , height (length) percentile, height (length) Z score, triceps skin fold thickness (TSF), TSF percentile, TSF Z score, mid upper arm circumference (MUAC), MUAC percentile and MUAC Z score] are measured at enrollment and 4 months after zinc supplementation (1mg/kg/day) and in thirty healthy children with matched age and sex (0.5-8 years). Serum zinc was measured by atomic absorption spectrometry.

**Results:** The mean initial serum zinc (±SD) in cholestatic, and healthy control group was 1251 ±558, and 1461±506 µg/l, respectively (P > 0.05). Meanwhile, serum IGF1 [median,(IQR),Range] in patients and control was 54(118),[10:780]ng/ml, and 250(387),[55:635]ng/ml respectively (P<0.001). No statistically significant difference was found between post Kasai patients and other cholestatic diseases. Children supplemented with zinc had their serum zinc 2223±1042 ug/l (P < 0.001) and IGF1 [median,(IQR),Range] 346(370),[50:825] ng/ml (P < 0.001). In addition, among Anthropometric variables, Height (Length) Z score and percentile were significantly improved (p <0.01).

**Conclusion:** As compared with the baseline, zinc supplementation had significantly Elevated serum zinc levels, IGF1 and improved growth in children and infants with cholestatic liver diseases. Thus zinc supplementation is beneficial for growth in infants and children with cholestatic liver diseases.

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Validity of the energy expenditure assessment by a multisensory armband accelerometer in 8-year-old children

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Objectives and Study: The aim of this study was to validate the ability of a multisensory accelerometer (Sensewear Armband 2, SWA) to assess Total Energy Expenditure (TEE) against the doubly labelled water method (DLW) in children.

Method: The TEE of fifty-six 8-year-old children from the European Childhood Obesity Project was assessed during the same time frame with the SWA (data processing with Professional InnerView software 6.1) and DLW. Available data was randomly assigned to a training (n=28) and an evaluation subset (n=28). The training subset was used to create a predictive equation by employing a linear regression model, with TEE from SWA as predictor and TEE from DLW as outcome, adjusted for gender. In the evaluation subset each child's TEE actually measured with the SWA and the one calculated by the predictive equation (TEE from SWA_{adjusted}) were compared to the TEE obtained by DLW using Bland-Altman plots.

Results: The SWA underestimated the TEE by 26±8% (mean difference= -473kcal; limits of agreement: -140,-807 kcal) when compared to DLW. When using the correction coefficient from the predictive equation on the evaluation subset, the agreement between TEE from DLW and TEE from SWA_{adjusted} was high, with a small overestimation of 4±8% (mean difference= 67kcal; limits of agreement: 351, -216 kcal) (Figure 1). The predictive equation was able to predict 53.3% (p< 0.001) of the TEE in the training subset, and 50.7% (p< 0.001) in the evaluation subset.

Conclusion: SWA algorithms obtained with InnerView Software 6.1 greatly underestimated TEE in 8-year-old children. This underestimation seemed systematically and thus applying a gender adjusted correction coefficient could help solving this problem.
**[Figure 1]**

A) Bland-Altman plot of the difference between TEE predicted with SWA and DLW against the mean of the two measurements. B) Bland-Altman plot of the difference between TEE from SWA adjusted by the predictive equation and DLW against the mean of the two measurements.

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Regional differences in childhood BMI data - the Malta Childhood National Body Mass Index Study

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Objectives and Study: Obesity is a problem of major public health concern all over the world and Malta has high obesity prevalence rates. With over a third of Maltese children being overweight or obese, the Malta Childhood National Body Mass Index study was devised to quantify the extent of the problem precisely. This paper looks at regional differences in the BMI data obtained.

Methods: Training in measurement was provided to physical education teachers and identical stadiometers were used. Data was processed using World Health Organisation cut-offs for underweight, overweight and obesity.

Results: A total of 41,343 students from 145 schools were measured. Age range from 4.7 to 17 years. Approximately 40% of school-aged children in Malta were overweight or obese, with higher percentages of obesity than overweight being observed. Results show significant differences in BMI between children living in Northern and Southern regions of Malta.

Conclusion: Results from this study further confirm the high levels of overweight and obesity in Maltese children. The North-South differences should help better target public health resources and should be further evaluated in more focussed research.

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Early nutritional programming: Effect of breastfeeding on Crohn’s disease natural history

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Objectives and Study: Recent increase in Crohn's disease (CD) incidence and changes in risk occurring with migration suggest a role for ambient factors in its pathogenesis. It has been described that environment influences disease risk through the gut microbiome. Breastfeeding (BF) is known to have potential benefits for infants due to the immunomodulatory properties of human milk, that also promotes intestinal homeostasis, regulates gut microbial composition, and modulates host gene expression. It has been published that being breastfed is associated with a decreased risk of surgery in adult patients with Crohn's disease. Our aim is to study the relationship between BF and the clinical severity CD in childhood.

Method: Data from CD patients under 18 years old was retrieved retrospectively from medical records. Study period 2000 - 2016. Disease severity was defined as the need for surgical intervention due to CD-related complications. Patients were labelled as cases or controls according to it. Exposure to human milk was considered positive if BF lasted more than 4 months. This was recorded by means of a telephone interview. The possible confounding effect of several CD features was studied: age at diagnosis, tobacco exposure and parameters considered by the Paris classification. Controls were selected on matching by frequency based in the characteristics that behaved as confounders. Odds ratio (OR), and its 95% confidence interval (95%CI), was calculated by multivariate logistic regression, with adjustment for matching covariates. Finally, a stratified analysis was also conducted to assess the interaction between BF and other factors influencing CD severity. Heterogeneity among strata was evaluated with the Wald test, considering a significance threshold at 0.1.

Results: Among the 133 CD patients included, 23 had surgery performed. Follow up period ranged between 2 and 17 years. Exposure to BF in CD patients who underwent surgery was found in 47.8% (95%CI 29.2% to 67.0%), while controls with this background were 74.6% (95%CI 65.7% to 81.8%). Four confounders were identified: upper digestive system involvement, isolated ileal disease (ILD), perianal affection and nonstenotic/nonfistulizing (or inflammatory) pattern. Frequency matching was carried out with a sample of 55 patients. Adjusted effect of BF over CD severity reached an OR = 0.36 (95%CI 0.10 to 1.27) with a p-value = 0.12. Inflammatory pattern (OR = 0.08) and isolated ileal involvement (OR = 4.53) significantly influenced the risk of surgery. BF increased the protective effect of the inflammatory pattern (OR change from 0.17 to 0.05) and decreased the effect of ILD (OR change from 6.50 to 3.47). However, the interaction did not reach statistical significance.

Conclusion: BF has not an independent early nutrition programming effect on the severity of CD. Nevertheless, it shows a tendency to favourably modulate the impact of truly risk factors for surgery.

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Iron deficiency anemia in infancy: evaluation of consequences in adult life

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Objectives and Study: Iron Deficiency (ID) and Iron Deficiency Anemia (IDA) are still prevalent health problems. Many studies relate ID and IDA to behavioral and neuro-cognitive consequences in infancy. However, little is known about the consequences in adult life, namely if iron supplementation resolves those consequences. Therefore we aimed to examine functional and neurocognitive outcomes, in adult persons who had IDA and ID in infants. Moreover, we wanted to evaluate whether there is a relation between those outcomes and iron status in infancy.

Method: We evaluated participants who were part of an observational study to evaluate ID/IDA in infancy from 1994. It included healthy infants born in 1994 (a total of 300 consecutive newborns, with 220 meeting the inclusion criteria, and 201 completing the initial protocol at 9 months). The infants with ID at 9 months (n=39) were treated with oral iron supplementation (3 mg/kg/day) and none was still with IDA after 3 months of therapy. They were submitted previously to evaluations (clinical and analytical) at 12, 15, 18 months and at 5, 8 and 11 years. At 9 months, the IDA children had development delay when compared with non IDA infants and after iron therapy, the general coefficient (GC) of the Griffiths test no longer showed significant differences. The eye-hand scale improved in IDA children and it was the only with a still significant difference at age eight. We contacted this participants at age 19-20 years for a presential evaluation, n=50. We assessed the following: education and academic achievement, biometric data like weight, height and blood pressure and mental and emotional health through the Beck Depression Inventory II (BDI II). Global health was measured using the SF 36-V2 Questionnaire. We used the Trail Making Test (TMT) for the neurocognitive evaluation, calculating direct and indirect adjusted scores. The evaluators of the neurocognitive test were blind to the iron status in infancy of the individuals. The IDA definition used was from the World Health Organization: in 9 month old infants haemoglobin (Hb) < 110 g/l with low ferritin. The ID definition used was ferritin < 12 ng/ml. The statistical analyse used t test and Mann-Whitney U in parameters without normal distribution (subscores of Health Questionaire). We also used ANOVA for a second analysis to compare the outcomes after dividing participants into 3 groups according to iron status.

Results: There were no differences in biometric data between groups. BDI II (p = 0.155) and SF 36-V2(p = 0.282) showed a tendency for better mental performance in the IDA group. There was a higher proportion of individuals not frequenting Superior Education in the IDA group (30.0%) comparing to the Control group (46.7%) (p= 0.377). There were no differences in total scores of the TMT part A (IDA: 28.2±2.7s Control:29.6±10.0s; p = 0.688) and part B (IDA: 84.7±39.5s Control:76.4±35.6s; p = 0.448) and in both direct and indirect adjusted scores. The correlation between ferritin levels at 9 months and adult performance was poor (r=0.002 p=0.989).

Conclusion: There are no differences in functional and neurocognitive performance between adults who had IDA at 9 months and the Control group. There is no correlation between iron status at 9 months and adult life performance.

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Prevalence and characteristics of malnutrition in hospitalised immigrant children

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Objectives and Study: Many childhood diseases influence nutritional status, including acute illnesses. Besides, being an immigrant child in a foreign country has also other burdens triggering malnutrition. Inadequate feeding, scarce of optimal dietary sources, poor housing and income decline are the most prominent causes for immigrant children’s malnutrition, escaping from war. In addition, nutritional status easily deteriorates even with a simple acute disease. The aim of the study is to evaluate the nutritional status of both local and immigrant paediatric inpatients.

Method: Hospitalized children aged 24 months to 72 months during March and April 2017 were recruited. Cases were divided into 2 groups as locals and immigrants. Nutritional risk was assessed with Paediatric Yorkhill Malnutrition Score (PYMS). Weight and height were measured within the first 24 hours after admission and upon discharge to calculate body mass index (BMI), weight for height (WFH) and height for age (HFA), z-scores were calculated according to WHO growth reference data. Demographic, socioeconomic and medical data was obtained by a questionnaire. No extra nutritional support during stay. Children with cerebral palsy and genetic syndromes were excluded.

Results: A total of 294 children (216 local, mean age: 42.4±21.6 months, 51.8% girls and 78 immigrants, mean age: 40.6±18.7 months, 53.8% girls) were eligible. Predominant reasons for hospitalization were respiratory and digestive diseases. Anthropometric data of the groups at admission is shown in table 1. Malnutrition frequency was higher in immigrants (14.4% vs 37.1%, p< 0.01) at admission. Immigrants were more prone to nutritional risk at admission (2.9±1.7 vs 4.6±2.1, p< 0.01). Length of stay was longer in malnourished children (median: 5 days in all patients, 3.2±2.8 days vs 5.5±3.1 days, p< 0.01) and also among immigrants 4.1±2.8 days vs. 7.6±3.3 days, p< 0.01). At the time of discharge, weight gain was insignificantly higher in immigrants (0.44±0.91 kg vs 0.86±0.83 kg, p>0.05).

<table>
<thead>
<tr>
<th></th>
<th>Locals (n=216)</th>
<th>Immigrants (n=78)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (z-score)</td>
<td>-0.13±0.76</td>
<td>-1.09±0.82</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>WFH (z-score)</td>
<td>0.19±0.93</td>
<td>-0.81±1.04</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HFA (z-score)</td>
<td>0.36±0.69</td>
<td>0.24±0.92</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

[Table 1 - Anthropometric data at admission.]

Conclusion: Our cohort suggests that majority of the hospitalized immigrant children are underweight and have acute malnutrition according to anthropometric measures. Besides, nutritional risk at admission to hospital is higher in immigrants. Malnutrition and being an immigrant is related with a longer stay in hospital.

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Validity and reliability analysis of the Turkish version of pediatric nutritional risk score scale

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Objectives and Study: Malnutrition contributes for 45% of child mortality under five years of age and is still an important public health problem in underdeveloped and developing countries. Hospital malnutrition is the malnutrition that develops during hospitalization even when a person is not malnourished when hospitalized. The rate of hospital malnutrition is also reported to be very high and it is approximately 20-50%. When the importance of malnutrition in inpatients is considered, the effect of scales in identifying this situation is quite high. We aimed to perform validity and reliability analysis of Turkish version of Paediatric Nutritional Risk Score (PNRS).

Method: Permission was received via e-mail to adopt the scale to Turkish. Forward and backward translations of the original scale were done. Following the consensus on translation, the scale went through the cognitive debriefing process. Then scale was performed on a group of patients. The study group was consisted of 149 patients aged one month-18 years with at least 48 hours of stay at hospital. Patients’ age, gender, anthropometric measurements, length of stay, admission diagnosis, daily body-weights, food consumption and pain status were recorded. Weight of the patients was measured daily. When the difference between the lowest weight measured during hospitalization or at the moment of discharge from hospital and the weight at the time of hospitalization was more than 2%, the patient was accepted as malnourished. To evaluate the validation of PNRS scale, the consistency of PNRS scores between two different physicians were assessed. Sensitivity, specificity, positive and negative predictive value were calculated.

Results: Of our patients 69 (46.3%) were girls, 80 (53.7%) were boys. The mean length of stay was 7.3 ± 4.0 days. Mean age of the patients was 51.9 ± 63.6 months (median 16.0 months). Fifteen patients had chronic and 30 had acute malnutrition on admission. According to PNRS scale 23 patients accepted to have high risk and 126 patients mild-moderate risk for hospital-related malnutrition. The weight loss was observed in 65.2% of patients in the high risk group and in 25.4% patients in the low-moderate risk group. The hospital malnutrition rate was 31.5%. Higher risk was identified in those with < 50% food intake and with more severe disease (p=0.006 and p<LT; 0.001, respectively). There was no difference between high and middle-low risk groups in terms of pain. PNRS’s specificity was 82.1%, sensitivity 77.8%, negative predictive value 92.0% and positive predictive value 58.3%. A good consistency suggests that Turkish validation was achieved successfully.

Conclusion: The good consistency between different practitioners refers to a successful implementation of PNRS validation. The power of PNRS to discriminate the patients with moderate-low risk of developing malnutrition is higher than patients with high risk. PNRS is considered a valid and reliable tool in establishing the risk for malnutrition in hospitalized patients.

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**Effect of Nutrition Friendly School Initiative on eating habits and anthropometry in school-aged children**

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**Objectives and Study:** In school age, eating habits and choices differ with the effect of both school and social environment. School has an important effect on development of food choices and growth of children. Improvement of school health is aimed with “Nutrition Friendly School Initiative” project by increasing sensitivity about healthy feeding and active life, and supporting procedures on this topic. In our study, evaluating the effect of “Nutrition friendly school initiative” project on eating habits and anthropometric values in school-aged children is aimed.

**Method:** A total of 516 school-aged children (2nd, 3rd and 4th grades) from two schools which is Nutrition Friendly and four schools which is not, are enrolled in our study. A questionnaire is applied to students in order to evaluate eating habits. Afterwards, weight and height of these children are measured by a digital weighing scale and a stadiometer. From these data weight and height z scores, weight for height percentages and body mass index percentages were calculated. “Children's Eating Behaviour Questionnaire” was answered by the parents. Eating habits and anthropometric values were compared between schools which are and are not nutrition friendly.

**Results:** A total of 516 school-aged children, of which 275 (49.8%) were girls and 259 (50.2%) were boys, were enrolled in our study. Age of the children was between 7-12 (mean 9.0±0.9) years. Most of the children were having regular mealtimes. Their families were also having breakfast regularly and preferring homemade foods. Most of the children had a tendency to consume vegetables, vegetable meals and fruits. Additionally they consumed fast foods and grocery foods less. Children brought to school “fresh fruits, homemade cakes-pastry, and milk” more and fast foods less for snacks. Students attending to nutrition friendly schools were consuming fruits more. On the other hand, negatively they were also consuming coke, chips, fast food and grocery foods more. Malnutrition was present in 102 (19.8%) of the children whereas 328 (63.5%) were normal and 86 (16.7%) were overweight and obese. Overweight and obesity were higher in students of not nutrition friendly schools, but this was not significant. Eating behaviors were not different with regard to being nutrition friendly. “Emotional overeating” scores were higher in girls.

**Conclusion:** “Nutrition Friendly School” project had a positive effect on eating behaviors of children, but no effect on anthropometric measurements. As students of 2nd–4th grade were enrolled, continuing nutrition friendly education might have positive effects on eating habits and obesity in long-term. In this age group, feeding is affected by family, media and social environment besides school. Therefore, besides supporting nutrition friendly school initiative, importance of the family and environment should be remembered, and education of the people responsible for feeding of the child should be taken in consideration.

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Development of a screening tool for oropharyngeal dysphagia in children with cerebral palsy

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Objectives and Study: To develop a screening tool for use in a community setting that can identify children with cerebral palsy (CP) who have oropharyngeal dysphagia (feeding and swallowing difficulties) impacting on feeding efficiency and safety, and may be at risk for undernutrition. Cross-sectional, observational study.

Method: Ethical approvals have been obtained. 69 children with CP between 2 and 18 yrs-of-age have been recruited and analysed. Average±SD age is 7.5±4.1 yrs, with the majority being male (67%). Gross Motor Function Classification System Levels were: I=19, II=24, III=4, IV=11, V=11. Predominant motor impairments were spasticity(n=46), dyskinesia(n=14) and hypotonia(n=8). Eating and Drinking Classification System levels (EDACS) included I=24, II=23, III=14, IV=5, V=3 with 40 children being independent feeders, 14 requiring assistance and 15 being totally dependent. Whilst children with feeding tubes were excluded, 32% of children had seen a speech pathologist/dietitian in the previous 12 months for feeding or nutrition concerns. Data collection for this study is ongoing.

Children attended a clinical mealtime evaluation which was digitally videotaped with a speech pathologist and dietitian. They consumed a range of age appropriate food and fluids including puree, lumpy-mashed foods, soft and tough chewable foods and thin fluids. Presence of oropharyngeal dysphagia (OPD) was rated using the Dysphagia Disorders Survey (DDS) using cut scores derived by Benfer et al (DMCN 2015, 57:358-365), direct observation of 17 clinical signs suggestive of pharyngeal phase dysfunction/aspiration including cervical auscultation, and if indicated sent for Videofluoroscopic Swallow Study.

Parents/caregivers were asked to answer a series of 31 questions based on Arvedson’s “Red Flags” (EJCN 2013, 67:S9-S12) related to their child’s feeding ability and nutritional status. The sensitivity (sn) and specificity (sp) of each question to identify children with OPD were calculated.

Results: Using the DDS cut scores, 49 children (71%) were defined to have OPD. Children were classified as having oral phase only (n=37,76%), pharyngeal phase only (n=1,2.0%) and combined oral and pharyngeal phase impairment (n=11,22%) with 11 children requiring VFSS and 17 children recommended to be on modified diets/fluids.

The questions with the highest sensitivity (sn (95% CI) and specificity (sp (95% CI) for identifying children with OPD are included in Table 1.
<table>
<thead>
<tr>
<th>Question</th>
<th>DDS</th>
<th>EDACS Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Se (95% CI)</td>
<td>Sp (95% CI)</td>
</tr>
<tr>
<td>Does your child cough during feeding or drinking?</td>
<td>0.62 (0.47 - 0.74)</td>
<td>0.70 (0.48 - 0.85)</td>
</tr>
<tr>
<td>Does at least one meal each day take more than 30 mins for your child to complete?</td>
<td>0.76 (0.62 - 0.85)</td>
<td>0.40 (0.22 - 0.61)</td>
</tr>
<tr>
<td>Does your child refuse food or drinks?</td>
<td>0.78 (0.64 - 0.87)</td>
<td>0.15 (0.05 - 0.36)</td>
</tr>
<tr>
<td>Would you describe most mealtimes as stressful?</td>
<td>0.52 (0.38 - 0.66)</td>
<td>0.72 (0.49 - 0.88)</td>
</tr>
<tr>
<td>I worry that my child does not eat enough food to grow properly.</td>
<td>0.62 (0.46 - 0.75)</td>
<td>0.53 (0.31 - 0.74)</td>
</tr>
<tr>
<td>Does your child have any problems eating compared to other children of his/her age?</td>
<td>0.63 (0.49 - 0.75)</td>
<td>0.80 (0.58 - 0.92)</td>
</tr>
<tr>
<td>Does your child have any problems drinking compared to other children of his/her age?</td>
<td>0.67 (0.53 - 0.78)</td>
<td>0.85 (0.64 - 0.95)</td>
</tr>
</tbody>
</table>

([Table 1])

Simple questions “Does your child have any problems eating compared to other children of his/her age?” or “Does your child have any problems drinking compared to other children of his/her age?” using a visual analogue scale (0-10) and “Does your child cough during feeding and drinking?” had the best combination of sensitivity and specificity for identifying children with OPD on both a standardised test of dysphagia (DDS) and using a functional classification system (EDACS).

**Conclusion:** Parent reported screening questions are a potential simple, low cost tool to identify children with CP at risk of oropharyngeal dysphagia. Following completion of data collection, further statistical analysis will determine which combination of questions has the highest sensitivity and specificity for identifying children requiring further assessment of oropharyngeal dysphagia.

**Disclosure of interest:** This research has received funding support from Nutricia. There are no other conflicts of interest.

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Evaluation of vitamin D levels in children and adolescents with cerebral palsy

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Objectives and Study: Vitamin D is essential for bone health. Children and adolescents with Tetraspastic cerebral palsy (TCP) have motor dysfunctions, which include disturbances in muscle tone and mobility. In addition, they can have convulsive syndromes and dysfunctional feeding. As there are several risk factors for bone health in this population, our objective was to analyse Vitamin D levels of children and adolescents with TCP.

Method: This is a cross-sectional study with a Group of TCP (n: 30) and Group of controls (n: 30). We studied levels of Vitamin D, gender, solar exposure, nutritional status, frequency of ingestion of vitamin-rich foods and constipation frequency between the groups ($\chi^2$-square/ Fisher's Exact Test). Vitamin D levels, gender, solar exposure, nutritional status, frequency of ingestion of vitamin-rich foods and constipation frequency, in TPC group. We compared levels of Vitamin D in TCP group and Controls Group (Spearman's correlation).

Results: There were no differences in gender, solar exposure, nutritional status, frequency of ingestion of vitamin-rich foods and constipation frequency between the groups. We didn't found differences between Vitamin D levels and gender, solar exposure, nutritional status, frequency of ingestion of vitamin-rich foods and constipation frequency in TPC group. Evaluation of use of anticonvulsivante was only possible for phenobarbital, due to the reduced number of other medications and there was no significant difference between the vitamin D values between users and non-users of phenobarbital (p=0.2392). There was no difference between enteral nutrition (gastrostomy ou nasoenteral probe) versus orally nutrition (p=0.2962). Vitamin D levels was not diferent among groups (p = 0.1711), the median of 25.30 ng / ml in the TCP group of cases and 29.70 ng / ml in the control group.

Conclusion: In our study vitamin D values did not differ between groups, but low levels should generate an alert that both healthy and TCP patients

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Nutritional state, food consumption and physical activity in a representative sample of young children from Sao Paulo, Brazil

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Objectives and Study: There is growing interest in investigating the prevalence and factors associated with obesity in children. Brazil is experiencing a nutritional transition characterized by a reduction in the prevalence of nutritional deficits and an increase in overweight and obesity. However, there are only limited data on activity level and dietary habits of Brazilian children. Our objective was to evaluate weight status, physical activity and screen time, food consumption patterns, and associated demographic characteristics of children in the metropolitan region of Sao Paulo, Brazil.

Method: A cross-sectional study in 1261 children aged birth-12y was conducted in the metropolitan region of Sao Paulo, including 788 1-12y olds. Participants were randomly selected and stratified by sex, age and social class. Measured heights and weights were used to calculate Body Mass Index and determine weight status (underweight, normal, overweight or obese), according to World Health Organization criteria (WHO, 2007). Physical activity and screen time were estimated using the Children Physical Activity Questionnaire adapted to the recommendations of the Brazilian Society of Pediatrics (SBP, 2008). Two non-consecutive 24-hour dietary recalls were conducted to estimate food intakes. Statistical analysis were performed using SPSS version 18.0.

Results: Among children in the metropolitan region of Sao Paulo, 30% of the toddlers (1-3 y) were either overweight (8%) or obese (22%). Prevalence of overweight or obesity was 40% in 4-6y children and 42% in children aged 7-12y. The toddlers were the least active, with 72% reporting low levels of physical activity. Children aged 4-6y and 7-12y reported higher levels of physical activity, with 67% and 81% (respectively) claiming more than 300 min per week of a range of different activities. Sedentary behaviors are a concern across all age ranges: 25% of 1-3y olds reported two or more hours of screen time per day. This was higher among 4-6y and 7-12y, with 47% and 50% reporting two or more hours of screen time per day, respectively. Looking at food groups, whole grain consumption ranged from 14-39%, with 4-6y olds reporting the lowest consumption. About 90% of children across all age groups consumed milk, but there was also high consumption of soft drinks (64% in 1-3y olds up to 91% in 7-12y olds). Only 70% of children reported consuming fruit. Potatoes were the most consumed vegetable (96-98% consuming on the day of the survey).

Conclusion: Child prevalence of overweight and obesity in Sao Paulo is high, toddlers reported lowest levels of physical activity, older children reported high screen-time, and food consumption patterns need improvement. Educational strategies are needed to reverse these trends, with opportunities for school-based interventions and improved parental education.

Keywords: Children, Obesity, Food consumption, Physical activity, Nutrition, Brazil

Disclosure of interest: Conflict of Interest Disclosure: The authors are employees of the Nestlé Research Center (NESTEC, S.A.), sponsor of this research.

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Anthropometry, body composition and functional performance in children with mild to moderate cerebral palsy in Recife, Northeast of Brazil

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¹Federal University of Pernambuco, Recife, Brazil

Objective: To evaluate the correlation between anthropometric and body composition parameters with functional performance in children with mild to moderate cerebral palsy.

Methods: A cross-sectional study examined 3 to 7 years of age children with cerebral palsy (CP) and mild to moderate motor impairment (I to III) according the Gross Motor Function Classification System (GMFCS). All of them were being assisted in regular motor physiotherapy program for, at least, 6 months and none had dysphagia or feeding difficulties. Mild CP was considered if GMFCS was I to II and moderate, if III. Weight and height were measured by standard techniques in them who could stand. Height was estimated by knee height in wheelchair users. The anthropometric parameters were classified as z-scores for age according to the WHO growth charts 2006/2007. Body composition (Body fat % and fat-free mass in kilograms) was measured by bio-electrical impedance using the four-electrode device Maltron BF-906Tm (Maltron, United Kingdom). The body fat index was calculated by the fat mass in kilograms/height in meters². Functional performance was assessed by the Paediatric Evaluation Deficiency Inventory (PEDI) and children continuous self-care and mobility scores were chosen for the analysis. Clinical variables (type of cerebral palsy, use of anticonvulsant drugs and age) and caloric/protein intake were controlled. The Pearson correlation coefficient (PC) was used to test the correlation between age, height, weight, fat-free mass, body fat% and fat-mass index with functional performance. A multivariate linear regression model to estimate the relation of the explanatory variables with functional performance was performed. The p < 0.05 was considered significant.

Results: Fifty-three children (age average of 4.5 years old, standard deviation of 1.2 years), 47 (83%) with spastic type, 32 with GMFCS I to II and 21 with GMFCS III were examined. Mild and moderate children were similar in age, type of cerebral palsy, caloric/protein intake and use of anticonvulsant drugs. All continuous variables presented a normal distribution according to the Kolmogorov-Smirnov test. The self-care functional performance was correlated only with fat-free mass in Kilograms (PC = 0.39) and age (PC = 0.36). The functional performance of mobility was inversely correlated with GMFCS III (PC = -0.65) and directly with height for age z-score (Table I). The fat-free mass maintained a significant positive correlation (beta = 0.28) with the functional performance of self-care, even age-controlled in the multivariate regression model (p = 0.5). The height correlation with mobility disappeared when it was controlled by GMFCS in a multivariate model.

Conclusion: In this study, fat-free mass was the only nutritional parameter associated with functional performance. Since functionality is strongly linked to health, these findings suggest that fat-free mass could be used as an important marker for nutritional surveillance in cerebral palsy children.
Table 1: Correlations between functional performance (FP) scores in self-care and mobility by Pediatric Evaluation Disability Scales (PEDS) with gross motor level, age, anthropometric and body composition parameters of 53 mild/moderate cerebral palsy Brazilian children.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Self-care FP</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Mobility FP</td>
<td>0.030*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. GMFCS mild/moderate</td>
<td>-0.131</td>
<td>-0.618**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Age in months</td>
<td>0.359**</td>
<td>0.140</td>
<td>0.118</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Z-score height</td>
<td>0.128</td>
<td>0.291*</td>
<td>0.332**</td>
<td>0.273*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Z-score weight</td>
<td>0.139</td>
<td>0.054</td>
<td>0.088</td>
<td>0.066</td>
<td>0.156**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Fat-free mass Kg</td>
<td>0.392**</td>
<td>0.208</td>
<td>0.192</td>
<td>0.196**</td>
<td>0.115*</td>
<td>0.724**</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Body fat %</td>
<td>0.03</td>
<td>0.141</td>
<td>0.282*</td>
<td>0.378**</td>
<td>-0.085</td>
<td>0.413**</td>
<td>0.389</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>9. Body fat/kg</td>
<td>0.025</td>
<td>0.156</td>
<td>0.313*</td>
<td>0.401**</td>
<td>-0.079</td>
<td>0.545**</td>
<td>0.341</td>
<td>0.865**</td>
<td>1</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level. **Significant at the 0.01 level.

**Mild = 1, 2 level and moderate=3 level according Gross Motor Function Classification System.

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Anaemia, a major nutrition problem - the impact of a Non-Governmental-Organization (NGO) actions in a poor region of Northeastern Brazil

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Objectives and Study: Anaemia is a global public health problem, not only as an indicator of malnutrition, poor sanitary and healthcare conditions, but also as a major burden to social and economic development. In Brazil, a systematic review of iron-deficiency anaemia has shown that its median prevalence was 59% in 2009, which is considered a high level by the World Health Organization (WHO). Brazilian Ministry of Health reported that, in children from 6 to 59 months, the prevalence of anaemia varies from 10% to 25%. Other authors have reported even higher rates in Northeastern states, where it may reach 92% in this age group.

The objective was evaluate hemoglobin concentration (Hb) in a pediatric population, between 6 months and 17 years old, living in a very low-income region in Northeastern Brazil. This population is attended by an NGO with projects in healthcare, nutrition and education.

Method: Along 3 days, a medical care task force took place in Catimbau, a remote poor area of Northeastern Brazil, to promote health assistance focusing on children. Hb of 296 children was measured using a point-of-care platform performed in capillary blood samples obtained by fingertip puncture. Anaemia was defined according to WHO criteria (2001). The following age ranges were used for data analysis: from 6 months to 4 years old; from 5 to 11 years old; from 12 to 14 years old and 15 years old or above.

Results: The overall rate of anaemia in this population was 12.83%. Only one child (1 yo) had Hb below 9 g/dL. Table 1 shows anemia frequency and mean Hb levels by age group.

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>6mo - 4yo</th>
<th>5yo- 11yo</th>
<th>12yo - 14yo</th>
<th>≥15yo</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER OF CHILDREN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>169</td>
<td>53</td>
<td>8</td>
<td>296</td>
</tr>
<tr>
<td>With anemia (%)</td>
<td>12 (18,2)</td>
<td>17 (10,1)</td>
<td>6 (11,3)</td>
<td>3 (37,5)</td>
<td>38 (12,8)</td>
</tr>
<tr>
<td>Hb level mean (g/dL)</td>
<td>11,9</td>
<td>10,9</td>
<td>12,9</td>
<td>13,5</td>
<td>12,6</td>
</tr>
<tr>
<td>Hb level median (g/dL)</td>
<td>12,1</td>
<td>12,7</td>
<td>13</td>
<td>13,5</td>
<td>12,6</td>
</tr>
</tbody>
</table>

Conclusion: Our results show a lower prevalence of anaemia in children when compared to previous reports in similar low-income populations, which observed rates from 25% to 92%. Severe anaemia (Hb < 9g/dL) was present in only one child. Although many factors might be related to this finding, it is possible that the presence of the NGO in this community, providing continuous access to nutritional, educational and healthcare programs, has promoted sensible improvement of childhood health status indicators.

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Introduction: Obesity and overweight prevalence has increased in the recent years. Several risk factors influence their development.

Objective: To identify risk factors associated with the development of obesity in preschool population.

Methods: Anthropometric data of children between 2-6 years of age were collected. Questionnaires about risk factors for obesity were applied to their parents. Statistical analysis of the results was performed running ANOVA and logistic regressions to identify the relationship between the different variables.

Results: 668 subjects participated. The prevalence of overweight and obesity was 10.93% and 12.87% respectively. The variables associated with obesity and overweight were: abdominal circumference percentile, tricipital skinfold percentile, body fat percentage and the level of physical activity. At age 4, other risk factors were associated such as the age of weaning, watching over 2 hours of television a day and the mother's education level. Starting on age 4, there was an spike in obesity prevalence.

Conclusion: This study showed that there are several preventable risk factors for the development of obesity in children. The results show that age 4 is a crucial age for the development of obesity, in which different environmental factors start playing a role. It is crucial to identify at an early age the risk factors that each child has, this way we could prevent the development of this disease, and its long-term consequences.

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Obesity associated with insulin-resistance and type 2 diabetes in children and adolescents

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Objectives and Study: Obesity is one of the main nutritional disorders in children and adolescents, with an importance increasing in countries with a higher live standard. There is an increasing pandemic incidence of obesity worldwide, with negative repercussions on the quality of life. The study aims are a retrospective evaluation of: obesity, degree of insulin-resistance and the incidence of type 2 diabetes in children and adolescents.

Method: We studied 185 patients aged between 6-17 years old, diagnosed with obesity, over a period of 3 years. Patients were divided into age groups: 6-10 years (group a = 33 patients), 10-16 years (group b = 95 patients) and over 16 years (group c = 57 patients). The patients and their caregivers completed a food questionnaire. Clinical data was based on evaluation of anthropometric parameters, as well as on determining the percentage of fat by impedance method-FAT. Biochemical investigations included lipid profile, glucose tolerance test, with HOMA index for determination insulin resistance.

Results: Higher incidence of obesity was found in girls (55%), while incidence was 45%, most of them from urban area (82%). In the age group 10-16 years were recorded most patients (52%), followed by group c-31%. The food questionnaire revealed daily consumption of: cereals with sugar (63.2%), sweets (73.7%), fast-food (69%). The mean value of FAT (normal value: 15.1-34%) was 39.2%, with a maximum of 48.2%, sustained by the value of waist circumference (mean value 92 cm). Metabolic syndrome, according to IDF criteria was found in 25% of patients. 75% had at least one cardio-metabolic complication such as: dyslipidemia (41.25%), hypertension (23%), impaired glucose tolerance (38%). 15% had hyperinsulinemia and 23% insulin resistance. 5 patients were diagnosed with type 2 diabetes.

Conclusion: Obesity is the preliminary step of metabolic syndrome and type 2 diabetes. Epidemic explosion of obesity among pediatric patients entails early implementation of clinical and metabolic screening methods.
NUTRITION - Nutrition and health outcomes

N-P-162

Dyslipidemia in children and adolescents with anorexia nervosa

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¹Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
²Clinical Hospital Centre Sestre milosrdnice, Zagreb, Croatia

Objectives and Study: Anorexia nervosa (AN) carries a risk for numerous metabolic complications, some of which can be lifelong, even fatal. Currently available data on causes and incidence of dyslipidemia in pediatric patients with AN are scarce. The aim of this study was to investigate the relation between the degree of malnutrition and endotype of eating disorder to dyslipidemia and circulating estradiol in patients with AN.

Method: This hospital-based study is a retrospective analysis of medical documentation of 183 female patients 7 to 21 years old (average 14,79±2,47) who were hospitalized in Centre for eating disorders in children and adolescents, Department of Pediatrics, Clinical Hospital Sestre milosrdnice, during a 10 years period (2005 to 2015).

Results: At admission average body mass index (BMI) was 11,30-20.03 kg/m² (15,77±1,93). The disease lasted for 0,7-108 months (12,8±13,9 months) at the time of diagnosis and the average loss of weight was 21,72±9,94 % in comparison to initial weight. Dyslipidemia, defined as total serum cholesterol >5.0 mmol/L was found in one third of AN patients (35.5 %). Worse anthropometric indicators and presence of amenorrhea at the time of diagnosis have proven to be in positive correlation to dysplipidemia (p=0,018 and p< 0,001, respectively). Furthermore, statistically significant higher levels of cholesterol were determined in patients who did not use laxatives (p=0,046) and who did not vomit (p=0,037) which demonstrates a correlation of dyslipidaemia to the restrictive endotype of AN (Table 1.) . No statistically significant correlation was determined between lipid profile and serum levels of gonadotropins or estradiol.

Conclusion: A negative correlation between elevated serum cholesterol and vomiting or usage of laxatives confirms starvation as a significant risk factor for development of hypercholesterolemia in patients with AN. Physical recovery, spontaneous menstrual cycle and normalization of attitude towards food are important objectives of treating AN, especially in order to avoid dyslipidemia as risk for future cardiovascular complications.
<table>
<thead>
<tr>
<th></th>
<th>BP (vomiting)</th>
<th>RT</th>
<th>t-value</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cholesterol average(mmol/L)</td>
<td>4,48</td>
<td>4,93</td>
<td>-2,12</td>
<td>98</td>
<td>0,037</td>
</tr>
<tr>
<td>triglycerides average (mmol/L)</td>
<td>0,95</td>
<td>0,96</td>
<td>-0,08</td>
<td>98</td>
<td>0,936</td>
</tr>
<tr>
<td>HDL average (mmol/L)</td>
<td>1,6</td>
<td>1,7</td>
<td>-0,72</td>
<td>98</td>
<td>0,470</td>
</tr>
<tr>
<td>LDL average (mmol/L)</td>
<td>2,6</td>
<td>2,8</td>
<td>-0,8</td>
<td>98</td>
<td>0,426</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BP (laxatives)</td>
<td>RT</td>
<td>t-value</td>
<td>df</td>
<td>p-value</td>
</tr>
<tr>
<td>total cholesterol average(mmol/L)</td>
<td>4,54</td>
<td>4,93</td>
<td>-2,06</td>
<td>110</td>
<td>0,046</td>
</tr>
<tr>
<td>triglycerides average (mmol/L)</td>
<td>0,98</td>
<td>0,96</td>
<td>0,44</td>
<td>110</td>
<td>0,657</td>
</tr>
<tr>
<td>HDL average (mmol/L)</td>
<td>1,61</td>
<td>1,72</td>
<td>-1,15</td>
<td>110</td>
<td>0,253</td>
</tr>
<tr>
<td>LDL average (mmol/L)</td>
<td>2,6</td>
<td>2,78</td>
<td>-0,75</td>
<td>110</td>
<td>0,452</td>
</tr>
</tbody>
</table>

[Average serum total cholesterol, LDL HDL and TG]

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Feeding/swallowing therapy among patients included in “Home Enteral Nutrition” (HEN) programme

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¹The Children’s Memorial Health Institute, Warsaw, Poland

Objectives and Study: Patients benefiting from enteral nutrition should be included in continuous, systematic feeding/swallowing therapy. Such care is essential for the purpose of maintaining swallowing activity, as well as providing a chance to increase the range of oral feeding along with growth of child’s chewing and swallowing abilities.

Intention of this study was to assess, whether children participating in oral feeding/swallowing therapy have higher share of oral food/fluids intake in overall nutrition, compared to children with no such an intervention.

Method: Patients with at least 50% of daily nutritional needs covered via enteral alimentation were included in the study. They were divided into subgroup of patients undergoing feeding/swallowing therapy (n=27) and subgroup without aforementioned care (n=88). Three aspects of oral feeding were compared between subgroups:

1. Progress in oral feeding range during 6-month period prior to the evaluation. (according to the parents judgement).
2. Assessment of the oral food intake.
3. Assessment of the oral fluid intake.

Data were collected through voluntary questionnaire, acquired during routine check-ups related to participation in “HEN” programme, and subsequently analysed with appropriate chi square tests to compare data distribution between both groups.

Results: Regarding to progress in oral feeding range, and oral food intake extent, there were no statistically significant differences between patients with or without feeding/swallowing therapy. However children benefiting from professional feeding/swallowing therapy statistically more often retain basic extent of oral fluid intake, compared to children without such aid. (63% vs 38.5%).

Conclusion: Presented outcome suggest that, attending professional feeding/swallowing therapy supports enterally fed patients in maintaining basal oral fluid intake rate. Simultaneously, there is no evidence that mentioned intervention has any measurable impact on oral food intake extent as well as, development of oral feeding/swallowing abilities.
Growth and body composition in children randomised to cow’s milk or a growing up milk between 1 and 2 years of age

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Objectives and Study: Nutrition in early life is a key determinant of immediate and lifelong health. Nutritional status must therefore be optimised during this period to support normal growth and development, to avoid long-term sequelae of sub-optimal nutrition. Early childhood is a period of time when nutrient deficiencies are prevalent. Growing Up Milk (GUM) also referred to as Follow-Up Formula for Young Children or Young Child Formula, was developed to assist young children in meeting their nutritional requirements during the dietary transition phase of the second year of life. However, there is limited evidence that GUM improves nutritional status, growth and developmental outcomes in young children. The aim of the Growing Up Milk-Lite (GUMLi) trial was to determine if consuming Growing up milk ‘lite’ (GUMLi) compared with standard cow’s milk as part of a whole diet for 1 year, provides benefits to nutritional status, cognitive development and body composition profile in 1-2 year olds.

Method: The GUMLi Trial was a multi-centre, double-blind, randomised placebo-controlled trial conducted in Auckland and Brisbane. Healthy children aged 1 year of age were randomised at to receive either GUMLi or standard cow’s milk (CM) for 12 months, as part of a whole diet. The primary outcome, reported here, was percentage body fat at 2 years of age measured by bioelectrical impedance. The secondary outcomes included measures of dietary intake (food frequency questionnaire and repeat record assisted 24 hr recalls); length, weight and waist circumference; micronutrient status (blood samples); and cognitive development using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley’s III). Anthropometric measurements were taken at 1 year of age and after 6 months and 12 months of the intervention. All regression models adjusted for baseline data and study centre.

Results: 160 children were enrolled and included in the primary intention to treat analyses. There were no significant differences between the two groups for any anthropometric data, ethnicity, mothers level of education, household income or any other demographic data at baseline after randomisation. There were no significant differences in weight, height or body mass index Z score between the two groups at 12 months follow up. The mean ± standard deviation (SD) of percentage body fat was 22.9% (± 8.2%) in the GUMLi group and 24.6% (± 8.3%) in the CM group. The adjusted group difference was -1.5% (95% CI: -3.7, 0.7; p=0.17). Sensitivity analyses excluding all data from participants with &LT; 10% body fat showed a significant group difference of -2.2% (95% CI: -4.2, -0.2; p=0.04) in favour of the intervention. The dietary energy intake at 12 months follow up was similar between two groups (4844± 861 kJ/d vs 4879 ± 895 kJ/d, p= 0.22) and the dietary protein intake was lower in the GUMLi group compared to the CM group (46 ± 10 g/d vs 51± 12 g/d, p= 0.02).

Conclusion: At 2 years of age children who consumed a GUM with a lower protein content compared to cow’s milk over 12 months had a lower percentage of body fat.

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Objectives and Study: Children who suffer from an excess of weight can be more predisposed to gastrointestinal disorders. The aim was to compare the main gastrointestinal diagnoses (GID) between overweight and obese patients in a pediatric nutrition and gastroenterology center between January, 2009 and June, 2015.

Method: Descriptive retrospective study in which the clinical records and the data base of patients with overweight and obesity were reviewed. The statistical analysis included the one-tailed chi square test with a significance of < p = 0.05.

Results: 222 patients were diagnosed as overweight and obesity, with ages of 1 to 233 months and a median of 71 months (IQR 19-124). 42.3% were obese. In overweight patients, functional constipation (57%) was the most frequent GID, followed by food allergy (16.4%) and gastroesophageal reflux (7%). In the obese group, functional constipation was also the most frequent GID (63.8%), followed by non-alcoholic steatohepatitis (6.4%) and food allergy (5.3%). Statistically significant differences were found between the diagnoses of functional constipation (p: 0.004), food allergy (p: 0.003), and gastroesophageal reflux (p: 0.011) on comparing the overweight group with the obese one (Table 1).

Conclusion: Functional constipation and food allergy were the most common gastrointestinal diagnoses in overweight and obese patients. Functional constipation was more common in the obese group, while food allergy was more frequent in overweight patients. Multiple gastrointestinal disorders are associated with the type of diet and the composition of the intestinal microbiota, among them functional constipation and food allergy. Healthy diet habits is a factor common and key both to establish a healthy microbiota and for the prevention and treatment of these disorders. Table 1. Gastrointestinal diagnoses in overweight patients in a pediatric nutrition and gastroenterology center (Gastronutriped) in Bogota, Colombia, 2009-2015.

<table>
<thead>
<tr>
<th>Gastrointestinal diagnosis</th>
<th>n</th>
<th>Overweight (%)</th>
<th>n</th>
<th>Obesity (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>73</td>
<td>57.0</td>
<td>60</td>
<td>63.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Food allergy</td>
<td>21</td>
<td>16.4</td>
<td>5</td>
<td>5.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>9</td>
<td>7.0</td>
<td>3</td>
<td>3.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Prolonged diarrhea</td>
<td>5</td>
<td>3.9</td>
<td>2</td>
<td>2.2</td>
<td>0.482</td>
</tr>
<tr>
<td>Eating behavior disorder</td>
<td>5</td>
<td>3.9</td>
<td>2</td>
<td>2.2</td>
<td>0.482</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4.2</td>
<td>-</td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
<td>1</td>
<td>0.8</td>
<td>6</td>
<td>6.4</td>
<td>0.566</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
<td>11</td>
<td>12</td>
<td>12.7</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>100.0</td>
<td>94</td>
<td>100.0</td>
<td>-</td>
</tr>
</tbody>
</table>

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**Complementary feeding using adult food and development of taste toward the Mediterranean diet**

Raffaella de Franchis¹, Raffaella de Franchis¹, Fabio Albano¹, Luigi Bozza¹, Pasquale Canale¹, Maria Chiacchio¹, Paolo Cortese¹, Antonio D’Avino¹, Maria de Giovanni¹, Mirella Dello Iacovo¹, Antonietta D’Onofrio¹, Aniello Federico¹, Nicoletta Gasparini¹, Felicia Iaccarino¹, Giuseppe Romano¹, Raffaella Spadaro¹, Mariangela Tedesco¹, Porfirio Toscano¹, Giuseppe Vitiello¹, Salvatore Auricchio², Dario Bruzzese³

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**Objectives and Study:** Taste development may be influenced by early exposure to natural flavours. Preference for tastes of the Mediterranean Diet (MD) may be kept over the years if these foods are early used in the complementary feeding. Objective of the present study is to verify the long term effect of weaning breast fed or formula fed infants using adult foods typical of the MD.

**Method:** A randomized controlled trial was carried out by 18 general paediatricians affiliated to the Italian Federation of Maedical Paediatrics (FIMP) of Naples. Exclusive breast fed or formula fed infants were weaned between 4 and 6 months of age, accordingly to the current guidelines. The weaning scheme was characterized either by industrial foods commonly used at weaning (controls) or by natural and seasonal foods as suggested by the MD (cases). Moreover, an adequate presence of fish, legumes, green vegetables, spices and aromatic herbs are early offered to children of the case group. Verbal reinforcement was carried out only in cases’ families at any visit in the paediatrician office to focus the mother attention on quality and quantity of food the kid is assuming and stressing the preventive role of MD to chronic-degenerative diseases. All mothers receive a questionnaire before the weaning (T0) and at 36 months of age of the kid (T36) to monitor eating family habits variations. Growing rates of children were regularly registered by the paediatrician. The explaining manual “MD in the first year of life” is freely given to all cases’ mothers. Data about MD adherence were collected by using questionnaires both for adult and for children (kidmed score). The primary endpoint of the study was the percentage of children with an optimal adherence to the MD (kidmed score >=8). The secondary endpoint was the longitudinal evaluation of the BMI. A further objective of the study was to register the familial eating habits in order to verify how many changes may come from an early education of the kid toward a Mediterranean eating style.

**Results:** 325 children (163 cases and 162 controls) have been enrolled. Preliminary results show a statistically significant association between mothers degree and their adherence to the MD. In contrast, no correlation was observed between mothers adherence to MD and birth weight of children. Interesting data come out from the analysis of mothers eating habits: about 100% of mothers regularly assume olive oil; in contrast only 40% assume three fruits per day and three portions of fish during the week. More than 80% of mothers does not regularly consume dried fruits and more than 50% regularly use commercial sweetened products. At 12 months of age, the kidmed score of the case group showed that 73,4% had a value between 8 and 12 (good adherence); 2,7% between 1 and 3 (bad adherence); 23.9% between 4 and 7.

**Conclusion:** The weaning time is a critical moment to have effects on children and familial eating habits. MD at weaning seems to be useful to have healthy habits at 12 months of age. In the next two years we will study both control and case groups to verify how useful are natural foods of the MD when early introduced with complementary feeding and which is their long term effects when compared to a traditional weaning.
Objectives and Study: To evaluate if there is an association between overweight, comorbidities and oral status in patients of a paediatric gastroenterology and nutrition unit.

Method: Oral status from 169 individuals between 11 and 18 years old was determined by a dentist using DMFT index (decayed, missing and filled teeth), bleeding on probing (BOP) test and visible plaque index (VPI). Rest salivary flow rate was evaluated during 5 min. The caries experience was classified as caries free (DMFT = 0) and caries experience (DMFT ≥1). According to the percentage of BOP (%BOP), periodontal disease (PD) was categorized as absent / mild (BOP < 10%) and moderate / severe (BOP ≥ 10%). The salivary flow rate was categorized as normal (≥ 0.7 mL / min) or decreased (< 0.7 mL / min). Weight and height were measured to calculate BMI, which was categorized as overweight (≥P85), obesity (≥P95), and severe obesity (≥120% P95) according to the CDC criteria. Associated comorbidities were based on insulin resistance - considering fasting insulin, HOMA-IR, C peptide and glycated hemoglobin - and cardiovascular risk criteria (lipidic profile, high-sensitivity C-reactive protein, fasting glucose and blood pressure). According to these, four groups were formed: A- No insulin resistance and no cardiovascular risk; B- No insulin resistance and cardiovascular risk; C- Insulin resistance and no cardiovascular risk; D- Insulin resistance and cardiovascular risk. The influence of age and gender were assessed separately. The statistical analyse used Kruskal-Wallis and Mann-Whitney tests.

Results: For the 169, 59.8% were male with mean (±standard deviation) age 14.2 (± 1.8) years. According to BMI, 40 (23.7%) were overweight, 88 (52.1%) obese and 41 subjects (24.3%) had severe obesity. Regarding to comorbidities, 30 (17.8%) patients were classified in group A, while 32 (18.9%) in group B, 44 (26.0%) in group C and 58 (34.3%) in group D. Five patients were not classified due to lack of blood analysis data. When evaluating the relationship between BMI categories and oral status, there were no significant differences regarding the DMFT index (p = 0.515), %BOP (p = 0.174), VPI (p = 0.103) and salivary flow (p = 0.069) (Table 1). In the same way, when compared the groups of comorbidities, the differences were not statistically significant for DMFT index (p = 0.855), %BOP (p = 0.234), VPI (p = 0.360) and salivary flow (p = 0.955).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Parameters</th>
<th>DMFT Index</th>
<th>Bleeding on Probing (%)</th>
<th>Rest Salivary Flow rate (mL/min)</th>
<th>Visible Plaque Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI categories</td>
<td>Overweight</td>
<td>BMI ≥ CDC 85th percentile</td>
<td>2.50</td>
<td>10.71</td>
<td>0.42</td>
<td>25.89</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>BMI ≥ CDC 95th percentile</td>
<td>2.00</td>
<td>17.86</td>
<td>0.28</td>
<td>27.88</td>
</tr>
<tr>
<td></td>
<td>Severe Obesity</td>
<td>BMI ≥ 120% CDC 95th percentile</td>
<td>1.00</td>
<td>21.42</td>
<td>0.26</td>
<td>33.48</td>
</tr>
<tr>
<td>p-value (Kruskal-Wallis Test)</td>
<td></td>
<td></td>
<td>0.515</td>
<td>0.174</td>
<td>0.069</td>
<td>0.103</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Group A</td>
<td>No insulin resistance and no cardiovascular risk</td>
<td>1.00</td>
<td>14.29</td>
<td>0.32</td>
<td>27.68</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>No insulin resistance and cardiovascular risk</td>
<td>2.00</td>
<td>22.25</td>
<td>0.24</td>
<td>33.80</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>Insulin resistance and no cardiovascular risk</td>
<td>1.50</td>
<td>19.64</td>
<td>0.28</td>
<td>32.72</td>
</tr>
<tr>
<td></td>
<td>Group D</td>
<td>Insulin resistance and cardiovascular risk</td>
<td>2.00</td>
<td>14.29</td>
<td>0.32</td>
<td>25.89</td>
</tr>
<tr>
<td>p-value (Kruskal-Wallis Test)</td>
<td></td>
<td></td>
<td>0.855</td>
<td>0.234</td>
<td>0.955</td>
<td>0.360</td>
</tr>
</tbody>
</table>

[Table 1]

There was a statistically significant difference between gender and DMFT (p = 0.033), VPI (p = 0.010) and the number of filled teeth (p = 0.020). Girls had a lower amount of plaque, however higher DMFT due to higher number of filled teeth when compared to boys. The number of decayed teeth (p = 0.104), missing teeth (p = 0.936) and the %BOP (p = 0.891) were not related to gender. Caries experience showed a significant difference in relation to the participants’ age (p = 0.018), showing an increase directly proportional to age. The PD (p = 0.670) was not associated to age.

Conclusion: This study suggests that different levels of excess weight and the presence of comorbidities are not related to the oral status, which may suggest that eating and hygiene habits may be more important than the direct influence of obesity, an inflammatory status, in oral status at that age level.

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Results of a psychological and nutritional group program in pediatric patients with inflammatory bowel disease

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Objectives and Study: Treatment adherence and healthy lifestyle in adolescent patients with chronic diseases are challenging. Psychological and behavioral therapies are highly recommended to reduce anxiety and depression, improving these issues. Furthermore, educational group therapies are useful to share fears and feelings with peers to cope with the disease. The main aim is to evaluate the efficacy of a psychological and nutritional group intervention program in IBD adolescent patients.

Method: Prospective pilot study evaluating a multidisciplinary program created ad hoc. The program involves 2 pediatric psychologists and a pediatric dietitian specialized in PIBD and includes 6 weekly sessions: 4 focused on emotional issues and 2 (involving patients and their parents) on nutritional aspects. At the beginning of the program, an evaluation of nutritional status was performed, including anthropometry, blood test and dietetic registration. State-Trait Anxiety Questionnaire (STAI) and EnKid Questionnaire were performed at the beginning and at the end of the program.

Results: Eight PIBD adolescent patients (aged 13-17 years old) were included (6 girls; 6 Crohn’s disease, 2 Ulcerative Colitis) and all of them completed the full program. At the end of the program, anxiety levels were reduced 50% according to the STAI questionnaire and adherence to Mediterranean diet increased from 30 to 60% according to EnKid Questionnaire. All participants evaluated the program positively and considered very beneficial the contact with PIBD peers.

Conclusion: A program focused on psychological and nutritional aspects is a useful intervention to reduce anxiety and to increase healthy nutritional habits in short-term follow-up. The program allows adolescent patients to acquire some coping strategies improving self-management on emotional and nutritional aspects. Medium and long term assessment is necessary to know the real impact of the program.

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Malnutrition and nutritional support practices in two outpatient clinics in a paediatric tertiary care center

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²Abbott, Istanbul, Turkey

Objectives and Study: To investigate the prevalence and severity of malnutrition as well as nutritional risk factors in Paediatric Gastroenterology (PGI) and Paediatric Nephrology (PN) outpatient clinics.

Method: Anthropometric measurements, nutrition practices (no nutritional support (NNS), supplementary enteral nutrition (SEN), exclusive enteral nutrition (EEN)), and records of 1593 children (girls: 44%) attending to our clinics between September 2015-July 2016 were analysed retrospectively. Height, weight, weight for height, body mass index (BMI) were analysed according to national standardised growth charts. Acute (AM) and chronic malnutrition (CM) definitions were based on World Health Organization (WHO) classification. Nutritional status was determined with Z scores The relationship between patients’ nutritional status, primary diagnosis and nutrition practices has been investigated.

Results: Mean age in the whole study group was 9.8 ± 5.2 years (range 45 days-20.5 years). The study group included 237 (14.9%) PN, 1356 (85.1%) PGI patients. Overall, acute and chronic malnutrition was observed in 457 (28%) and 692 (44%) children respectively. Severity of acute malnutrition was classified as severe in 2% (n: 39), moderate in 7% (n:117) and mild in 19% (n:301) in the whole group. In the PGI group AM was observed in 381 children (24%). Severity of AM in the GI group was as follows: 2% severe (n: 35), 6% moderate (n:100), and 16 % mild (n:246). Among the children visiting PN outpatients clinic, AM was observed in 75 patients (0.2% severe (n:4), 1% moderate (n:16), and 3% (n:55) mild) When severity of CM was assessed in the whole group, 22% of the patients had mild CM (n:348), 13% had moderate CM (n:204) whereas 8.8% had severe CM (n:140). In PGI group CM was evident in 36% (n:574, mild in 18% , moderate in 12% ,severe in 6%) . CM rate was lower (8 %) in children attending PN outpatients clinics (n:117, mild in 4 %, moderate in 1 %, severe in 2%). Among the whole study group, overweight and obesity rates were 26% (n:412) (overweight 10%(n:164), obese 16%(n:248).

On assessment of malnutrition according to the primary diagnosis, frequency of AM was highest in children with neurological disorders (51 %), chronic liver disease (LD) 48,3%(cholestatic LD 26,7 %, non-cholestatic LD 21,6 %) and malabsorption syndromes % 32,8. Obesity and overweight was found higher in the hepatosteatosis group (84 %) as expected.

In our study group, nutrition practices were as follows: 82.1% (n:1309) on NNS, 14.8% (n:236) on SEN, and 3% (n:48) on EEN. Malnutrition rates were also assessed according to the nutrition practices in PGI and PN groups separately: Rates of AM & CM in PGI group were 15.6% & 23.4 % in NNS, 12.2% & 9.4% in SEN, and 2.08% & 2 % in EEN subgroups respectively . Rates of AM & CM in PN group were, 17.7% & 23.4 % in NNS, 0.9 % & 9.4 % in SEN, and 0.06 % & 2 % in EEN subgroups.

Conclusion: Acute and chronic malnutrition is a problem in children followed in the outpatient clinics. Malnutrition rates are influenced by outpatient nutritional practices. Children on exclusively enteral nutrition had lower rates of malnutrition. Increasing awareness with more diligent solution strategies may change the current status of acute and chronic malnutrition.

Disclosure of interest: This study was supported by Abbot Nutrition.
Developmental and cognitive profile of children with intestinal failure

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Objectives and Study: Children with intestinal failure (IF) are at risk for neurocognitive problems due to several underlying factors such as malnutrition, preterm birth, low birth weight and prolonged hospital stay. In addition, the treatment of intestinal failure-associated liver disease minimises parenteral lipid intake, further raising suspicion of inadequate nutritional support for neurodevelopment. Few previous studies in the neurodevelopment of IF patients exist and they are composed of small and selected patient groups. These studies did not detect major developmental problems, although the cognitive capacity of IF children lagged behind that expected in the general population.

Method: We contacted paediatric-onset IF patients seen in our institution and invited them to participate in the current cross-sectional study including assessment of cognitive and motor skills using validated tests (WPPSI-III, WISC-IV) with established normal reference values. Psychological tests covered linguistic index (LI), visual index (VI) and intelligence quotient (IQ), while motor development was assessed with the Movement ABC test. We also assessed patient characteristics, underlying diagnoses and nutrition.

Results: The participating 22 patients had a median age of 7.7 years (range 3-16), median gestational age (GA) of 33 weeks and median birth weight of 1410 grams. GA was below 28 weeks in six patients. Most frequent diagnosis was short bowel syndrome (n=17), followed by intestinal dysmotility syndromes (n=4) and congenital enteropathy (n=1). Four children currently received parenteral nutrition, whereas eighteen had full enteral nutrition. Median duration of parenteral nutrition was 9.9 months. Ten (45%) children had previously been diagnosed with neurological difficulties. Three children were not able to complete linguistic tests and one did not complete the visual test. LI, VI and IQ scores were low average or very low in 37%, 24%, 37% and extremely low in another 37%, 43%, 37% of the patients, respectively. Table 1 shows the distribution of neuropsychological test results. In addition, movement ABC test found 33% of the children having significant and 14% having minor movement difficulties.

<table>
<thead>
<tr>
<th></th>
<th>131- Extremely High</th>
<th>121-130 Very high</th>
<th>111-120 High Average</th>
<th>90-110 Average</th>
<th>80-89 Low Average</th>
<th>70-79 Very low</th>
<th>69 Extremely low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linguistic index</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual index</td>
<td></td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Intelligence quotient</td>
<td></td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: This study indicates that children with IF have a high risk for neurodevelopmental difficulties and should be monitored closely during childhood to ensure early support for those lacking behind.

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Associations between postnatal growth rate and cognitive outcomes at age 16 years in infants born small-for-gestational-age at term

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Objectives and Study: Rapid post-natal growth (RPNG) is associated with increased risk of adult cardiovascular and metabolic disease. In preterm infants, RPNG is also associated with improved long-term cognition. Small-for-gestational-age (SGA) term infants have increased risk of adverse long-term cognitive outcomes compared to appropriate-for-gestational-age infants; they are also prone to rapid post-natal ‘catch-up’ growth. It is therefore important to understand whether RPNG in this population confers any long-term cognitive advantage, and balance this with recognised metabolic risks. In this study we investigated associations between post-natal growth in term-SGA infants and cognitive outcomes in adolescence.

Method: Weight, head circumference (HC) and length were measured in 60 term SGA infants (birthweight< 10th centile) from a larger prospective intervention study at enrolment, 6, 12 and 26 weeks, 9 and 18 months; with follow up at age 16y. Measurements were converted to standard deviation scores (SDS; UK-90) and changes in SDS between different time points were calculated. Cognitive outcomes were measured at 16y to assess global intelligence (FSIQ, VIQ, PIQ (WASI)); and literacy and academic attainment (Wechsler Individual Attainment Test (WIAT)-reading and maths subtests). Associations between growth and cognitive outcomes were explored in univariate and multivariate analyses.

Results: Mean cognitive scores were significantly higher than the population mean apart from VIQ. From birth-18 months weight-gain, HC and linear growth were faster than the reference population, most significantly in the first 6 weeks. In univariate analyses HC growth from 0-6 weeks was significantly associated with higher FSIQ and VIQ: a 1-SDS increase in HC growth was associated with 7.10-point higher FSIQ (95% CI 1.15, 13.04, p=0.02) and 10.82-point higher VIQ (95% CI 3.31, 18.34, p=0.006). However, after adjustment for confounders (birthweight, gestation, infant diet, maternal age, education smoking, socioeconomic status), HC growth no longer significantly predicted outcome (adjusted difference FSIQ 1.91 (-3.5, 7.3); VIQ 4.0 (-2.7,10.7)), whilst higher maternal education was a significant positive predictor of IQ, reading and maths scores. No significant associations between weight or length gain or HC gain during other periods and cognitive outcomes were found.

<table>
<thead>
<tr>
<th>Test</th>
<th>Unadjusted mean (SD)</th>
<th>p (compared to population reference 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIQ</td>
<td>104.4 (17.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>PIQ</td>
<td>104.3 (10.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>FSIQ</td>
<td>104.8 (13.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>WIAT Reading</td>
<td>105.8 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WIAT Maths</td>
<td>105.2 (19.2)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Conclusion: Head growth from birth to 6 weeks was positively associated with later IQ but this was not significant after adjustment for confounding factors, possibly related to the small sample size. Maternal education was the most significant predictor of cognitive outcomes at 16y. Given recognised metabolic risks associated with RPNG, this study does not support the promotion of rapid growth in term-SGA infants. However, this needs to be confirmed in a larger sample.

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Observational study of the dietary management of constipation in infants between the age of 1 and 2

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Background: The benefit of fiber-rich diets remains discussed for management children constipation and dietary measures alone are not recommended as first-line treatment (1) but little data is available on daily dietary management of constipation in infants.

Objective: To describe the dietary management of constipated children between the age of one and two and to assess the impact of fiber enriched formula (FEF) on constipation at the age of two in real life settings.

Method: Prospective cohort study of one year old children requiring dietary management of constipation according to their pediatrician. Two cohorts (FEF and control) were followed-up to the age of two.

Results: 494 patients (314 FEF, 180 control) were recruited and 366 assessed at the age of 2. Both cohorts were similar in terms of characteristics at birth and at inclusion. At the age of two, only 5% of FEF and 7% of Control patients still had ROME IV constipation (NS) and quality of life (QUALIN) improved (+8.7 vs +6.4 points, NS) in both cohorts. Significant differences (p<0.001) in favor of FEF were found for the improvement of stools consistency according to the Bristol score (85% vs 64%), fear of defecation (28% vs 59%), pain at defecation (27% vs 47%), abdominal pain (29% vs 60%), bulky stools (49% vs 71%) and bloating (42% vs 57%). Similar proportions of patients had changed their formula during the year of follow-up (14% vs 12%, NS).

Conclusion: Constipation at the age of one is improved by dietary measures. The use of FEF significantly improved constipation related digestive symptoms at the age of two compared to control patients.


Disclosure of interest: This study has been funded by Blédina (Danone)

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The early development of lifestyle-related diseases is already evident in obese children in primary school

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Introduction: The prevalence of obesity has increased during the past decades, in children as well as in adults. Childhood obesity increases the risk of lifestyle-related diseases such as non-alcoholic fatty liver disease (NAFLD), diabetes, cardiovascular disease and renal disease. To lessen the impact on individuals and society, it is necessary to reverse these diseases at the earliest possible stages.

Method: The early development of lifestyle-related diseases was evaluated in 306 school-aged children (46% boys; 153 primary school children (6-11 years) and 153 secondary school children (12-16 years)) with obesity (59%) or morbid obesity (41%). The effect of a family based, interdisciplinary lifestyle intervention on these early aberrations was evaluated in 84 primary school children and 76 secondary school children.

Results: Elevated liver transaminase levels were already present in 53% of primary school children with obesity. Insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension were present in respectively 47%, 2.4%, 49% and 7% of primary school children. The presence of glomerular hyperfiltration in 25% of primary school children demonstrates that organ function is already affected at a young age. The prevalence of these disturbances did not differ significantly between primary and secondary school children, except for a higher prevalence of glomerular hyperfiltration in primary school children and a higher prevalence of insulin resistance in secondary school children.

After one year of lifestyle intervention there was a significant improvement of BMI z-score (-0.25 ± 0.31), LDL cholesterol (-0.30 (IQR -0.70;0.10)), systolic blood pressure z-score (-0.31 ± 1.26) and estimated glomerular filtration rate (-7.27 (IQR -16.85;4.75)) in primary school aged children. For BMI z-score, LDL cholesterol and systolic blood pressure, the positive effect of the intervention was significantly greater in primary school children compared to secondary school children.

Conclusion: The early development of lifestyle-related diseases, including NAFLD, is already evident in primary school aged children with obesity and morbid obesity. The positive effect of lifestyle intervention on these early aberrations is greater in primary school children compared to secondary school children, reflecting the need to start intervention as early as possible.

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Routine newborn screening for MMA - What are the implications?

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Objectives and Study: Routine newborn screening programme for metabolic disorders like Methyl Malonic Acidemia (MMA) - is it worth the effort and money in India, though it is an established practice in many parts of the world.

Subjects and interventions: Newborn screening for metabolic disorders was performed on samples obtained from various hospitals in South India between 19th January 2007 and 19th September 2017. Dried blood samples from either heel prick or venepuncture were collected @ 36 hours of age from babies, on special filter papers, dried & sent in for analysis by Tandem Mass Spectrophotometry (TMS).

Results: In the study period, a total of 54,426 samples were obtained. From these samples received from various hospitals, abnormal results were detected in 221 (0.41 %). These samples had mild elevation in both propionyl-carnitine (Normal range being 0.3-4.2 µmol/L whole blood) and methylmalonic acid (Normal levels < 1.10) that at levels often associated with a maternal vitamin B12 deficiency, but not indicative of MMA. Hence all these abnormal samples parents were counselled, maternal vitamin B12 levels checked and given injection of Vitamin B12 and Newborn Screening test was repeated after 3 weeks in the babies - and all the 221 samples were NORMAL when this analysis was repeated on these babies.

Conclusions:
1) The incidence of most of the inborn errors of metabolism is unknown in India.
2) Incidence of MMA was “thought to be higher” in the past, but no accurate estimations are available.
3) In our study the incidence of “Pseudo MMA” was shown to be nearly 0.5% which hitherto could have been “interpreted as MMA” accounting for the belief that MMA is higher in incidence in India.
4) Untreated and undetected these “pseudo MMA” can manifest themselves as various disorders in infancy including “Infantile Tremor Syndrome”
5) Further studies in large multi centre involving many more babies is required to ascertain the same in different parts of India.

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Finding an effective and safe cholecalciferol dose for the prevention and treatment of vitamin D insufficiency in children under three years of age

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Objectives and Study: Was to analyze the efficacy and safety of different doses of aqueous cholecalciferol (CCF) in the prevention and treatment of vitamin D insufficiency in young children.

Method: A total of 247 infants and children aged 1 month to 3 years, residing in the Russian Federation were evaluated: 104 subjects (42.1 %) in their first year of life, 81 (32.8 %) in the second, and 62 (25.1 %) in the third. Baseline serum 25(OH)D concentrations were determined. After that, patients were administered CCF for 30 days at different doses, based on their serum calcidiol level: 4000 IU/day for patients with 25(OH)D levels of less than 10 ng/mL, 3000 IU/day for those with concentrations in the range of 10 to 19 ng/mL, 2000 IU/day for levels in the range of 20 to 29 ng/mL, and 1000 IU/day for concentrations exceeding 30 ng/mL. A follow-up laboratory examination was carried out after 30 days of vitamin D supplementation. The subjects were divided into three groups on the basis of the CCF dose expressed per kg of body weight: Group 1 - 104 patients given CCF doses of less than 150 IU/kg/day, Group 2 - 109 children receiving doses in the range of 150 to 300 IU/kg/day, Group 3 - 34 subjects administered CCF doses of more than 300 IU/kg/day.

Results: The median (Me [25Q - 75Q]) baseline calcidiol level in the analyzed group was found to be 29.1 [22.4 - 42.8] ng/mL. After one-month cholecalciferol supplementation, the serum 25(OH)D concentration increased 1.5 times from baseline, being 47.9 [37.3 - 64.7] ng/mL (p<0.0001). The calcifediol concentration increased from 42.1 [32.5 - 51.3] to 43.3 [34.5 - 52.9] ng/mL in patients who had received vitamin D doses of less than 150 IU/kg/day, from 25.3 [21.5 - 29.3] to 48.9 [40.9 - 65.6] ng/mL in subjects given 150 - 300 IU/kg/day, and from 15.5 [12.0 - 25.2] to 69.9 [46.5 - 99.3] ng/mL in children given doses of more than 300 IU/kg/day (p<0.05, p<0.0001, p<0.0001). A direct correlation was observed between the plasma calcidiol concentration and the cholecalciferol dose per kg of body weight, r = 0.64, p< 0.0001. Fig.1 presents a comparative analysis of vitamin D content in patients administered one-month supplementation with aqueous CCF solution. There were stable proportions of deficiency and insufficiency < 20 ng/mL, as well as satisfactory levels in the range of 30 - 100 ng/mL, in Group 1 subjects. In Group 2, a statistically significant increase in the proportion of children with sufficient vitamin D content (p< 0.0005) was observed, as the proportion of patients with calcidiol concentrations exceeding 100 ng/mL slightly increased. In Group 3, similarly to Group 2, CCF supplementation was shown to be highly effective; however, serum calcidiol concentrations of more than 100 ng/mL were detected significantly more frequently in subjects given vitamin D doses exceeding 300 IU/kg*day (p< 0.05).
Conclusion: A dose of less than 150 IU/kg/day was found to be prophylactic (per kg of body weight). The dose range from 150 to 300 IU/kg/day may be regarded as the optimal therapeutic interval, because these doses produce a significant improvement in the vitamin D status without increasing the risk of overdose. Administration of doses exceeding 300 IU/kg of body weight per day may result in serum calcidiol concentrations higher than the threshold of 100 ng/mL.

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The Relationship between Vitamin D levels and Lipid profiles in non-obese children

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Background: Vitamin D deficiency has been associated not only with cardiovascular disease itself but also with cardiovascular risk factors, such as obesity, hypertension, dyslipidemia and hyperglycemia. Some studies report on the association between vitamin D level and dyslipidemia among obese children. But it is thought to be natural that in obese children, low vitamin D level be associated with hyperlipidemia. So the objective of this study was to investigate the relationship between serum vitamin D level (25-hydroxyvitamin D, [25(OH)D]) and lipid profile in non-obese children.

Methods: The study was carried out from March to May 2017. Total 376 healthy volunteers, aged 9 to 18, were enrolled in our study. They underwent blood test necessarily including vitamin D, triglyceride (TG) and high density lipoprotein cholesterol (HDL-C). 25(OH)D, as the primary circulating form of vitamin D, could be regarded as the indicator of serum vitamin D level. In this study, only non-obese children, defined as BMI < 23kg/m², was 243 (64.6%). We divided subjects into two groups; vitamin D deficiency (25(OH)D < 20ng/mL) or normal (25(OH)D ≥ 20ng/mL). Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) software version 24. Student's t-test and simple linear regression analysis were used to estimate the association between vitamin D level and lipid profile.

Results: The mean of 25(OH)D in 243 non-obese children was 17.27ng/mL (4.4-43.0ng/mL). There was no difference to age or sex. And the mean of serum TG levels in same subjects was 85.54mmol/L (28-346mmol/L). The vitamin D levels were inversely associated with TG (β coefficient = -1.506, p < 0.001) and TG/HDL-C (β coefficient = -0.041, p < 0.001). To investigate whether the relationship between serum 25(OH)D and lipids differs by vitamin D level, we categorized the participants into two subgroups of vitamin D deficiency and normal. The overall percentage of 25(OH)D less than 20ng/mL was 69.5%. Vitamin D deficient group had higher TG levels than normal group (90.27 vs 74.74mmol/L, p = 0.013). In addition, this tendency also appeared on TG/HDL-C (1.753 vs 1.358, p = 0.018).

Conclusions: Vitamin D level influences lipid profile, even in non-obese children. Vitamin D could reduce synthesis and secretion of TG by regulating intestinal calcium absorption. Therefore, Vitamin D deficient children had higher TG values and might progress to dyslipidemia or obesity. So maintaining normal vitamin D level seems to have a benefit on lipids.

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Objectives and Study: Several studies have already demonstrated a significant association between an increased cardiometabolic risk and sedentary behaviors, such as the number of hours in front of a screen, in pediatric age. However, in studies that only used samples of obese children and adolescents, the results were inconsistent. So, the aim of this study is to examine the relationship between screen time and cardiometabolic risk factors, and search for differences between two measuring methods of the screen time, a written and an oral one.

Method: For this study, we used data from the Pediatric Gastroenterology and Nutrition Unit from a tertiary hospital, that follows prospectively overweight and obese children. For this study, we excluded all the children and adolescents with no screen time measures. The variables used were Gender, Body Mass Index, Glycated Hemoglobin, Total Cholesterol, HDL Cholesterol, Triglycerides, Fasting Insulin, Metabolic Syndrome (defined by International Diabetes Federation) and Number of Hours in front of the screen. The screen time was measured by one of two methods, an oral in the moment of the appointment and a written record (daily in a week at home). The statistical analyses involved Mann Whitney U tests. The association between screen time and cardiometabolic risk was evaluated with a multiple linear regression. The relationship between Metabolic Syndrome and screen time was assessed separately using simple linear regressions.

Results: From 1603 children and adolescents followed, 307 (2-18 years) had screen time measures. Of these, 162 were female (53%). Through the Mann Whitney U test, only Triglycerides (Median(Md)=74.0 mg/dL; Minimum(Min)=24.0; Maximum(Max)=416.0) had statistically significant differences between each gender (U=11.6; p=0.02), with higher values in females. Age (Md=10.0 years; Min=2.0; Max=18.0) was the only variable with a statistically significant relationship (B=0.3; p<0.01) with screen time (Md=15.8 hours; Min=0.3; Max=75.0 hours), in which the higher number of hours belonged to the older ones. The screen time and the Metabolic Syndrome didn’t show a statistically significant association. Concerning the measurement of screen time, statistically significant differences were found between the oral (n=94; Md=20.5 hours; Min=0.3; Max=75.0 hours) and the written records (n=214; Md=14.0 hours; Min=0.3; Max=66.5; 81% missing), p&LT; 0.01.

Conclusion: Although it was expected more reliability with the written method, the oral one showed more efficiency, with higher adherence and reported hours. Then, it’s advisable to use an electronic format to assess the sedentary lifestyle or, if not possible, it should be used an oral method, at the time of the appointment. In this sample, age was the only variable with significant relationship with screen time. It showed that the older ones spent more time in front of the screen, which is similar in non-obese children. Metabolic Syndrome didn’t have a significant relationship with screen time, but this might be related to the fact that our sample was composed by a pediatric population. Then, it would be interesting to evaluate screen time registry in these pediatric population would have repercussions in the future.

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Probiotics and acidified infant formulas as a potential cause of D-lactic acidosis in infants and children - a review

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Objectives and Study: Extensive research ongoing in the field of probiotics and infant formulas raises a number of safety questions. One such concern is the potential influence of D-lactic acid-containing preparations on the health of infants and children. This review aims to summarise the available knowledge on the ingestion of D-lactic acid-producing bacteria and acidified infant formulas as a potential cause of paediatric D-lactic acidosis.

Method: We conducted a Medline database search using keywords such as lactic, lactate, acidosis, microbiota, probiotics, Lactobacillus, Bifidobacterium, child, infant, newborn, and toddler in various combinations. The bibliographies of identified papers were screened in search of additional references. We also contacted experts in the field of probiotics and infant food research to identify grey literature related to the subject.

Results: We identified 5 randomised controlled trials (RCTs) that included D-lactate concentration measurement and lactic acid-related outcome assessment in infants receiving D-lactic acid-producing probiotic strains. In general, no clinically relevant adverse effects of the interventions were observed. The only cases of paediatric D-lactic acidosis described in the literature occurred in children suffering from short bowel syndrome, and only in 2 of them was the occurrence of acidosis reportedly preceded by the administration of probiotics. Concerning the use of D-lactate-containing infant formulas, 3 out of 4 identified experimental studies from the 1950s and 1960s revealed that dietary intake of lactic acid in neonates and infants in the form of acidified milk formulas leads to metabolic acidosis and a decrease in weight gain; however, none of these studies were randomised or placebo-controlled. Among currently available infant formulas, the ones that may contain the most significant amounts of lactic acid are fermented infant formulas. In a recent meta-analysis of RCTs, no negative health effects of their use were documented.

Conclusion: Overall, none of the RCTs included in this review showed any risk of using D-lactic acid-producing bacteria as probiotics in healthy infants. Historically, use of acidified milk formulas may have led to metabolic acidosis and a decrease in weight gain. However, currently used fermented infant formulas do not seem to have a negative influence on infant health.

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Nutritional status of vegetarian children: Russian experience

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Objectives and Study: Interest in the vegetarian diets has increased in Russia lately. As vegetarianism represents certain risks of micro- and the macronutrients deficiency in children the study of their nutritional status is of current concern. Objective - to determine the nutritional status of children on vegetarian and other non-conventional diets.

Method: The study was carried out in “National medical research center of children's health” on 130 children aged 1-17 years. Their nutritional status was evaluated based on the results of clinical laboratory tests and anthropometric measurements (ANTHRO+) in correlation with their diet.

Results: Anthropometric measurements data were within the normal limits in 94% of children; low body weight - in 3%, overweight - in 0,7%, low height - in 2,3%. Assessment of diet revealed lower than normal energy intake in 21,5% and higher - in 30,7%; insufficient protein intake - in 33,8% of children. Biochemical laboratory findings showed protein deficiency in 1,5% of children, iron deficiency - in 20,7%, iron deficiency anemia - in 15,4%, zinc deficiency- in 18,1%, high serum zinc - in 53,3%, normal serum calcium in all children. Vitamin B12 deficiency associated with lack of animal protein in the diet and supplementation was found in 29,2%, marginal level - in 23,8%. Only 15,4% of all children used vitamin B12 supplements.

Conclusion: The results of the study demonstrate that the nutritional status of vegetarian children should be closely monitored by the pediatricians and nutritionists. These findings also indicate that there is an urgent necessity to work out relevant Nationwide Guidelines.

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Exploring the factors that may contribute to nutrient intake in the paediatric intestinal transplant population. A mixed method study

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Objectives and Study: The factors that may contribute to children struggling or successfully transitioning from tube to oral feeding after intestinal transplantation are unclear. Feeding difficulties are common after transplant with many children who should be able to eat needing tube feeding for an extended period. There is a suggestion from intestinal failure literature that aversive experiences and early feeding disruption may be influential. However, there is little evidence on factors influencing eating in intestinal recipient children and no qualitative or mixed method approaches have been used. The purpose of this study was to explore factors that may contribute to nutrient intake after intestinal transplant. An understanding of these factors could help manage caregiver expectations and if eating difficulty predictors could be identified earlier, targeted interventions could potentially be facilitated.

Method: A sequential explanatory mixed method study using postal questionnaires and food diaries followed by telephone interviews was used to explore factors impacting on nutrient intake. Caregivers of the entire UK paediatric intestinal transplant population (n=34) were invited to participate in the quantitative component (questionnaire, food diary) while the qualitative (interview) sample (n=8) was drawn from survey/food diary respondents expressing an interest in participating. The questionnaire consisted of feeding and demographic items and the Children’s Eating Behaviour Questionnaire (CEBQ). The three-day food diary was a record of all food and drink consumed, converted to nutrient intake using Nutritics software. Analysis was by descriptive statistics using SPSS. Semi-structured telephone interviews explored caregiver perceptions of their child's eating, analysed thematically.

Results: The survey response rate was 26% (n=9) with 89% (n=8) also being interviewed. Median nutrient intake was 93% (range, 61-137) of estimated energy requirements. There was a statistically significant association between eating well after transplant and pre-transplant eating (having solids in infancy (p=0.012), significant practice eating (p=0.012), positive eating experiences (p=0.012)) (Figure 1).
CEBQ-measured approach/avoidant behaviour was also statistically significantly associated with post-transplant nutrient intake (p=0.048). Those classified as food approach were more likely to be meeting requirements than those classified as food avoidant. Qualitative data were grouped into three themes: medical, other and child influences on eating. Factors which emerged in the interviews as influential on post-transplant eating included: being nil-by-mouth, aversive experiences, transplant timing, caregiver influence, the child's influence and professional input.

**Conclusion:** This study provides the first empirical evidence of an association between pre-transplant eating and nutrient intake. The mixed method approach provided an opportunity to understand quantitative findings from this study. The findings suggest the importance of promoting pre-transplant eating and supporting caregivers and indicate that there may be eating difficulty predictors that could be used to facilitate targeted interventions - further research is required.

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The knowledge gap in food portion sizes for children aged 1-3 years

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Objectives and Study: Obesity is a global epidemic that poses future catastrophic public health outcomes. Healthy weight is achieved in only 40% of the Irish population and 25% of children are categorized as being either overweight or obese. Obesity is now occurring in early childhood and the trajectory then tracks into adulthood. Establishing a healthy diet from an early age is fundamental in the prevention of obesity. Our aim was to establish what knowledge parents and various health care professionals working with children had in relation to appropriate portion sizes of different food groups for pre-school children.

Method: Parents of children attending outpatients and healthcare professionals working with children were invited to complete a pictorial questionnaire on what they regarded as appropriate sized portions for the main food groups for children aged between 1-3 years. Healthcare professionals asked to complete survey included Paediatric Nurses, Non-Consultant Hospital Doctors, Consultant Paediatricians and Dieticians.

Results: In total 50 parents of children aged 1-3 years and 50 healthcare professionals completed the questionnaire. Only 54% of parents (n=27) who completed the questionnaire answered the correct amount of milk a pre-school child should receive under normal circumstances. Correct daily portion size of vegetables was identified by 56% of parents (n=23) and healthcare professionals (n=23). We asked “From what age is it advisable that you stop offering milk in a bottle?” 2/3 (n=34) of parents answered correctly but only 1/3 (n=19) healthcare staff got the question right. The majority of parents 50% (n=25) stated Doctor or Public Health Nurse as their information source about portion size for their children but 34% of health care professionals (n=17) acknowledged that they did not know about any resources on appropriate portion sizes in this age group.

Conclusion: We identified a knowledge deficit regarding food portion sizes for this age group. Parents frequently ask healthcare professionals for guidance about healthy diet, therefore a better proficiency in dietary advice and readily available resource tools in the clinical setting may be highly beneficial.

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Examining nutritional habits and the use of supplements in women during pregnancy in comparison to existing recommendations - a cross-sectional survey

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Objectives and Study: The diet and nutritional state of women during the pregnancy period have major implications not only on her health but also for her infant’s. There are official recommendations for nutrition during pregnancy, which are endorsed by the Israeli Ministry of Health, that includes emphasis on certain diet ingredients and the use of suitable dietary supplements. The purpose of the current study was to characterize certain dietary elements and the use of dietary supplements among pregnant women in relation to the official recommendations, and whether these characteristics are related to socio-economic status (SES).

Method: A cross-sectional survey, by interviewing mothers attending family health centers (FHS) in different areas of the city of Tel Aviv, Israel.

Results: 239 mothers were recruited, from whom half reported on being informed of the guidelines for dietary changes during pregnancy, 30% were informed by a professional source. Lower consumption of raw meat and higher consumption of fish and seafood were found among higher SES compared to low and intermediate SES (p=0.002, p=0.03, respectively). Most participants did not increase their intake of food items enriched in Calcium or Iron during pregnancy, regardless of their social status. Ninety four percent of subjects reported on being informed of the guidelines for dietary supplements during pregnancy. In comparison to subjects of high or intermediate SES, those of low SES were less compliant with the recommendation for Folic acid supplementation (p=0.02) and less likely to use other dietary supplements such as a multi-vitamin and Omega 3 during pregnancy (p=0.01, p&lt;0.001).

Conclusion: There are certain deficiencies in the awareness and implementation of medical guidelines to nutrition during pregnancy, and gaps between women of different socio-economic status, mostly in the use of dietary supplements.

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Galectin - 9 as a new biomarcer for the diognosis of lactose malabsorption in children’s obesity with polymorphisms of the lactase gene

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Objectives and Study: To investigate the association of mRNA expression of galectin - 9 (Gal - 9) and lactose malabsorption in children's obesity with polymorphisms (SNP) of the lactase gene (LCT).

Methods: The study involved 78 children with obesity (BMI>97 percentile) aged 6-18 years. The definition of SNP LCT (material for investigation - venous blood), expression of Gal - 9 mRNA (material for investigation - buccal epithelium) by real-time polymerase chain reaction analysis, the study of lactose malabsorption by Hydrogen breath testing. The first group of observations was presented by 40 children with genotype C/C 13910, the second group consisted of 38 children with phenotypically identical genotypes C/T 13910 and T/T 13910, p>0.05.

Results: Genotype C/C 13910 was registered in 40 (51.3%), genotype C/T 13910 in 28 (35.9%) and genotype T/T in 10 (12.8%) patients. Lactose malabsorption in children with genotype C/C 13910 averaged 32.7±10.4 pmm, in children with genotypes C/T 13910 - 26.3±4.9 pmm (p>0.05) and with genotype T/T 13910 - was absent (p&LT; 0.05). The average expression level of Gal - 9 mRNA in children with genotype C/C 13910 was 564.6±35.8 relation units ΔmRNA Gal - 9/mRNA actin, in children with genotypes C/T and T/T 13910 - 61.0±15.8 relation units ΔmRNA Gal - 9/mRNA actin, p&LT; 0.01. It is important that the lowest mean level of expression of Gal - 9 mRNA (42.47±13.4 relation units ΔmRNA Gal - 9/mRNA actin) was recorded in the subgroup of children with genotype C/C 13910 and lactose malabsorption (n=22), whereas the largest mean level of expression of Gal - 9 mRNA was recorded in the subgroup of children with the C/C 13910 and without lactose malabsorption (n=18) - 1086.73±51.2 relation units ΔmRNA Gal - 9/mRNA actin, p&LT; 0.01.

Conclusion: The expression level of Gal - 9 mRNA depends on lactose malabsorption in children with genotype C/C 13910.

Keywords: galectin - 9, obesity, children, malabsorption of lactose.

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Randomised trial testing new complementary feeding guidelines: effects on food consumption and growth at 6 years of age

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Objectives and Study: In a RCT (randomised control trial) testing new complementary feeding guidelines in Colombian infants with an emphasis on fruit, vegetable and meat consumption and continued breastfeeding in seventy-six 6-12mo old infants from Bogota, Colombia, we found positive effects on haemoglobin concentrations and on food consumption at age 12mo¹. In this follow-up study, we investigated whether the intervention had longer-term effects on food consumption and growth.

Method: Children from the RCT were followed up at age 6-7 years. Weight and height were measured and converted to Z scores for age (HAZ (height for age Z score), BMIZ (body mass index Z score)) using WHO (World Health Organization) growth reference data. Food consumption was assessed using a food frequency questionnaire. Data on total breastfeeding duration was recorded

Results: 65.8% (50/76; 50% boys) of the children from the RCT participated; 54%(27/50) from the control group (CG) and 46%(23/50) from the intervention group (IG). There was a trend towards longer total breastfeeding duration in IG children than those in the CG (26 mo (±SD12.8) versus 20.8 (±8.8) months, p=0.07). There were no significant differences in the frequency of consumption of fruit, vegetables, meat or milk between groups although the trend was for more frequent consumption in the IG. Chocolate milk drinks consumption was significantly higher in the CG than in the IG (5.9 (±5.1 versus 3.4 (±2.4) times per week; p<0.05) but there was no difference between groups in the consumption of fruit juices or fizzy drinks.

HAZ at 6 years and change in HAZ from 6mo-6 years were lower in the IG (HAZ score -0.91 (±0.9) versus -0.16 (±0.91), p=0.006; change in HAZ (IG 0.35 (0.67), CG 0.57 (0.68), p=0.27). However after adjustment for length at 6mo and maternal height (CG 158.3 cm (±5.4) v IG 153.7cm (±5.9), p<0.05), the difference in HAZ was not significant. BMI Z score was 0.17(±0.84) in the IG versus 0.41(±0.99) in the CG (p=0.37). The proportion of overweight (>1 ≤2 Zscore) and obese children (≥2 Zscore) was non-significantly higher in the CG (overweight 18.5% versus 13%; obesity 3.7% versus 0.0%).

Conclusion: Despite a trend towards lower BMI and a lower proportion of overweight/obese subjects in the IG, differences were not significant. Similarly, whilst there were trends suggesting more frequent consumption of fruit, vegetables, meat and milk in the IG, the only significant difference was a lower consumption of chocolate milk drinks. The follow-up was limited by the small sample size. Furthermore, any effect of the intervention on food consumption may have been masked by the fact that the children's diets were significantly influenced by food and drink provided at school rather than by their family.


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Obesity, feeding practices and parental perception of the child’s weight, a Mexican survey

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Objectives and Study: Since Mexico takes the first place in childhood obesity worldwide, this study explores the eating habits in a mexican population in order to describe the feeding practices that influence the child’s nutritional status and the parents’ perception about their child’s appearance.

Method: After the correspondent validation study of the Comprehensive feeding practices questionnaire (Cronbach’s alfa 0.7), consisting of 35 items from 11 feeding habits, an observational, analytic and transversal study was performed, including parents of children aged 2 to 6 years. They were surveyed, according to the spanish version of the questionnaire. Demographic data was collected, parents’ perception was defined with the 2003 Scott Millard pictograms and body mass index (BMI) was measured from both parents and children. Parents selected the sketch that most resembled to the child’s silhouette, according to the panel of 7 figures for each gender, that represented the percentiles ranges for low weight (&LT;5), normal weight (5 to &LT;85), overweight (85 to &LT;95) and obesity (≥95). Linear regression was used to examine the variables that influenced the 11 feeding practices, through multivariate analysis of variance (MANOVA) and post hoc follow-up tests.

Results: There were 154 valid responses gathered, including mostly mothers (n=125, 81%), coupled parents (n=133, 86%), workers (n=98, 63%), with higher education (n=136, 88%) and normal weight (n=89, 57%). Children were 53% males and 47% females with a median age of 46 months (SD ±15) and a prevalence of 20% of overweight/obesity was reported in this study (n=31). Parents of overweight/obese children were more likely to restrict the food consumption with the aim of limiting the less healthy foods and sweets (p<0.014), decreasing or maintaining the child’s weight (p<0.016) and promote the intake of less variety of nutrients and well-balanced food (p<0.03); 80% underestimated their nutritional status (n=25/31). Parents that perceived their children with normal weight (n=127, 82%) were less likely to pressure the child to eat (p<0.038) and those who perceived them overweight (n=8, 5%) also restricted them for weight purposes (p<0.015). Parents whose perception corresponded to the child’s nutritional status (n= 106, 68%) were more likely to actively demonstrate healthy eating for the child (p<0.038).

Conclusion: The spanish version of the Comprehensive feeding practices questionnaire represents an adequate instrument to assess feeding practices in parents of children aged 2 to 6 years. Mistaken perception of the child’s nutritional status is a current matter in mexican population: few parents recognized their children as overweight/obese, so that pictograms might not be the best way to estimate obesity when physical measurements are unavailable. Feeding practices such as restriction for health or restriction for weight control are recognized behaviors in parents of overweight/obese children, that are modifiable through interventional measures.

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Association between environmental determinants and intestinal microbiota structure in the development of atopic dermatitis in infants at high risk of atopy

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Objectives and Study: Atopic dermatitis occurs mainly during the first year of life. Parental atopy is significantly associated with the manifestations and severity of AD, but environmental factors may play a role. The Prebiotics in Prevention of Atopy (PIPA) project aims to evaluate the effects of early nutrition on atopic dermatitis (AD) and to investigate the factors that may influence atopy onset in a population of infants at high risk of atopy.

Methods: The time of onset of AD was evaluated using a Cox regression model in a population of 540 infants with at least one atopic parent. Intensity was assessed by the Scorad score. The final model included the following covariates: type of feeding (breastfed-BF, prebiotic formula fed - PF, standard formula fed), sex, home pets, total number of children in the household, father’s education level, smoking during pregnancy and age at introduction to solid food. A total of 201 and 199 infants were randomized to receive a PF and standard formula (SF), respectively; 140 infants remained on exclusive breastfeeding until 12 months (BF). A substudy was conducted to evaluate gut microbiota composition in 147 infants (45%). Stool samples were collected at baseline (before starting the nutritional intervention, with age ranging from 1 to 6 months) and at 9-12 months of age. Gut microbiota composition was investigated using fluorescence in situ hybridization.

Results: 41% of patients developed atopic dermatitis in the first year. The mean number of AD episodes was 5.03 ± 9.6 and the mean duration was 9.65 ± 8.3 days. No difference in the number of patients developing AD was observed between infants fed formula milk and those breastfed. Among children who developed AD, the vast majority of the SCORAD scores were below than 15 until 24 months of age. SCORAD score during all observation period significantly decreased (p: 0.004) without any difference between the two groups. An increased risk of AD was found in infants born to cesarean section than in those born naturally (p: 0.018). According to the Cox model, the rate of AD was reduced by 35% in PF compared with SF (p: 0.09) and by 38% in BF compared with SF (p: 0.001). Among the considered covariates, ‘age at introduction of solid food earlier than 6 months’ was significantly associated with higher risk of AD in children (p: 0.03).

Infants free from AD (n = 78) had a lower F/B ratio than No AD (n= 69 ) at baseline (p:0.012). Clostridium difficile colonization did not correlate with occurrence of AD in the 2 first years of life (p: 0.09). At post-intervention, AD-free infants had a significantly higher colonization with Clostridium cluster I (p: 0.02) than the AD group. The rate of respiratory infections and use of antibiotics was higher in children with AD (p:0.003 and p:0.02, respectively). Bifidobacteria load was significantly lower in infants that received antibiotics at least one course (p 0.007).

Conclusion: Cesarean delivery, early nutrition, time of weaning and antibiotic use are the main environmental risk factors of AD in the first two years of life. They probably act through the perturbation of intestinal microbiota. Modulation of these risk factors remains the most important way for primary prevention of AD in particular in patients at risk.

Disclosure of interest: The study was full founded by Mead & Johnson Nutrition. (NCT02116452).

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The relative risk of dyslipidemias with respect to waist-height ratio and body mass index in obese paediatric patients

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Objectives and Study: Aim objective was to measure the strength of association between anthropometrics parameters and dyslipidemias to identify the relative risk of developing dyslipidemia in obese patients. The functionality of study was of a descriptive type, the temporal sequence was of a transversal type, the control of the assignment of the study factors was an observational type and the beginning of the study in relation to the chronology of the events was retrospective.

Method: 714 patients from 4 to 18 years old with obesity from the National Institute of Paediatrics in Mexico, were evaluated. The waist-height ratio (W/H ratio) tool was defined as >0.50 and Body Mass Index (BMI) as >2 SD. The values for the lipoprotein profile were according to ATP III. Triglycerides were evaluated at (>100 mg/dl) for < 10 years old and (>130 mg/dl) for >10 years old. The confidence interval (CI) for the relative risk (RR) was 95% using Software IBM SPSS Statistics V.24.

Results: Children with a waist-height ratio >0.50 have 1 to 3.4 more risk of presenting clinical dyslipidemias, mainly triglycerides, LDL-C and 2.35 times more likely to present atherogenesis and early cardiovascular risk.

Conclusion: Paediatric patients with exogenous central obesity (W/H >0.50) have a higher risk of presenting dyslipidemias than those with only BMI >2 SD. Dyslipidemia is a risk factor for cardiovascular disease, early detection by way the waist-height ratio and early treatment it could prevent metabolic complications in adulthood.

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**Obesity in childhood and adolescence. Evaluation of a therapeutic model based on a frequent clinical intervention**

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**Objectives and Study:** To evaluate the impact of an intervention model based on the promotion and reinforcement of healthy habits for the treatment of obesity and its complications in children and adolescents. Exploratory, descriptive, prospective and longitudinal study.

**Method:** The study population consists of a total of 27 individuals between 5 and 18 years old who attended for the first time to the Obesity and Adolescents Clinic of the National Institute of Paediatrics (COAINP) with a diagnosis of overweight (Z score of Body Mass Index [BMI] above +1 Standard Deviation [SD] and up to +1.99 DE for age/sex) and obesity (BMI Z score above +2 SD for age/sex) according to international standards without presenting any intercurrent pathology. The intervention design consists on a basal consultation in which they were evaluated by a multidisciplinary health team. Subsequently, a weekly consultation was granted up to a total of 8 reviews, followed by a monthly consultation up to 6 times to complete 8 months of total intervention. The clinical indicators evaluated and registered in each consultation were: total body weight, waist circumference, eating patterns, medical-nutritional treatment follow-up and psychosocial evaluation.

**Results:** The average result of the study revealed a decrease of 2.23 kg of total body weight, 3.68 cm of waist circumference and an important adherence to the recommendations of healthy habits in the first 8 weeks with respect to the baseline values. The final result after 8 months of intervention revealed an average decrease of 931g of total body weight, the value of the waist circumference was maintained at 3.67cm less than the baseline and good maintenance was shown in the attachment to healthy habits.

**Conclusion:** Successful treatments for obesity are limited. Intervention models based on constant and frequent surveillance seem to facilitate adherence to recommendations, obtain results of lifestyle improvement and perpetuate the result for periods longer than half a year. In the present study, the work on the ability to acquire healthy habits, shows a clear relationship between positive results with the weekly frequency of intervention, while the spacing of consultations slows down the beneficial result. It is important to distinguish that the model used in this study, in addition to achieving good results, is easy to replicate, adapt and develop viability at all levels of care in Mexico.
Habit Formation

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Iron deficiency and iron deficiency anemia in hospitalized infants aged 1 to 36 months in Northern Italy: An observational study

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Objective and Study: In infants and toddlers iron deficiency (ID) is the most common cause of anemia and should require a careful surveillance and dietary supplementation. Recently a study found a prevalence of ID from Western Europe of 11.8%. Known risk factors for ID include early cord clamping, exclusive use of breast milk after 6 months of age, low socioeconomic status, low dietary intake, prematurity, and low birth weight.

Objective: To assess iron deficiency anemia (IDA) and ID in hospitalized infants aged 1 to 36 Months in Northern Italy with an observational study.

Methods: The prevalence of ID and iron deficiency anemia (IDA) have been evaluated in 450 hospitalized infants, admitted to hospital for common disease, aged 1-36 months of life, in Northern West Italy from December 2015 to December 2016. Complete blood count and ferritin evaluation were performed, and type of feeding and risk factors were assessed. IDA was defined as haemoglobin (Hb) levels < 110 g/L and ID as serum ferritin < 12 µg/L in the absence of infection (high sensitivity C-reactive protein < 10 mg/L), according to WHO definitions. All statistical analyses were conducted using SPSS software (release 19.0, SPSS, Inc., Chicago, IL). We used t tests for continuous measures and X² for categorical data to describe and compare cohorts. Associations between feeding pattern and iron status were analyzed using X² and logistic regression.

Results: Complete data were obtained from 450 infants: 56.2% boys, mean (SD) age was 6.5 (5.8) months. The prevalence of IDA was 10% IDA, with a mean age of 7.7 months, and Hb levels of 98.3 (6.0) g/L. The prevalence of ID was 3.7%, with a mean age of 8.6 months, and Hb levels 113.4 (2.7) g/L. The prevalence of IDA in preterm infants was 4%, with a mean age of 2.5 months, and Hb levels 95.0 (8.0) g/dL. None of patients with IDA/ID received iron supplementation before hospitalization. Identified risk factor have been prematurity, chronic severe disease, high weight growth rate. Considering Hb and ferritin levels according to feeding pattern in infants < 6 months, we found higher values of Hb in breastfed infants than artificially fed ones (11.7 vs 10.7 g/dL; p<.05). Ferritin values was higher in Breastfed infants than artificially fed (11.6 vs 10.5 µg/L µg/L; p<.05).

Conclusion: Our findings showed that IDA/ID are still prevalent in hospitalized children aged 1 to 36 months in Northern-West Italy. The observational nature of our study cannot establish a causal relation between breastfeeding and iron deficiency/IDA, however exclusively breastfed infants showed in the present study higher Hb and ferritin levels than formula fed infants in the first 6 months of life. Actually current nutritional recommendations and habits are inadequate for the prevention of ID and IDA. Protocols for detecting and preventing ID/IDA in early infancy are needed, especially to prevent minor cognitive, motor, and social-emotional development as well as neurophysiologic alterations.
The influence of maternal anthropometric measures, levels of vitamin D and adiponectin on anthropometrical measures and bone health in offsprings

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Objectives and Study: From conception onward, a child is developing under the influence of a series of biological events, which enable maturation of tissues, growth and adaptation. This multifactorial process represents the interplay between genetic, environmental and dietary influences. The aim of this study was to assess the impact of maternal pregnancy body weight (BW), vitamin D and adiponectin status on offspring growth and bone health.

Method: 141 healthy pregnant women (mean age 30.6, SD +/- 4.2 years) and their singleton newborns were included in the study performed from May 2011 to June 2012. In the 32nd week of pregnancy anthropometric measurements were performed, serum was collected and frozen at -20°C until 25(OH)D and adiponectin were measured by radioiodine (¹²⁵I)-based radioimmunoassay and ELISA based method respectively. Anthropometric measurements of their offspring (BW, length (L) and head circumference (HC)) were performed at birth and at the age of one and three years. Bone health at birth was evaluated with quantitative ultrasound at the right tibia by measuring two parameters: speed of sound (SOS, in m/s) and as standard deviation relative to normal controls (Z-score).

Results: A statistically significant correlation was found between the mother’s BW and offspring’s BW at birth (p < 0.01) and BW up to three years of age (p &LT; 0.05). A statistically significant correlation was found between mother’s BW and offspring’s HC (p &LT; 0.05) at birth and HC until three years of age (p &LT; 0.05).

Vitamin D deficiency was present in 14.4% and insufficiency in 40.9% of pregnant women. There was no significant association between maternal 25(OH)D and anthropometrical measures in offsprings at birth (BW p=0.35, L p=0.59 and HC p=0.47). There was a significant negative correlation between a maternal serum adiponectin and offspring’s BW at birth (R= -0.37, p=0.002); H (R= -0.31, p=0.008) and HC (R= -0.29, p=0.014). There was no significant correlation between maternal 25(OH)D levels during pregnancy and SOS in newborns (p=0.48). Additionally, a correlation between maternal adiponectin concentration during pregnancy and SOS in newborns was not significant (p=0.82).

Conclusion: Our study indicated that maternal weight in pregnancy was associated with the growth of their offsprings in the first three years of life. Although a high prevalence of low vitamin D level among pregnant women was found, maternal vitamin D status did not influence growth and bone health of their offsprings. Maternal circulating adiponectin levels in plasma showed an inverse relationship with anthropometrical measures of infants at birth, while no correlation with the newborns' bone health was found.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia and is in accordance with the Declaration of Helsinki.

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Antibiotic exposure in the first three years of life and weight gain during childhood

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Objectives and Study: Childhood obesity has become a global epidemic and represents a significant burden for the public health system, due to its direct correlation with overweight in adulthood and due to possible adverse health implications. According to the data obtained from National Health Survey, Slovenia is following this trend. While genetic transmission of risk of overweight and obesity from parents to children is well established, various environmental factors are involved as well. The composition of gut microbiota in overweight and obese children has recently received particular attention. Therefore, the aim of our study was to investigate whether early exposure to antibiotics (< 3 years of age) influence child's risk of overweight at 8 years of age.

Method: Our retrospective, case-control study included 477 school children and was performed at Primary care Medical Centre Maribor, Slovenia. The study was approved by the by the Institutional medical ethics committee. Children's anthropometric measurements, body height (cm) and body weight (kg) were collected during the regular school systematic screenings at 8 years of age. A total of 73 of these children (15.3%) were overweight with their BMI between 85th and 95th percentile for age and sex. The control group (N=367) consisted of children within normal BMI range (5 - 85th percentile) for age and sex, who were randomly selected out of the pool of all observed records. Information regarding the child's weight, height, age and area of their school was taken during their physical examination. The additional data on height and weight at the age of 3y and 5y as well as nutritional remarks, information about breastfeeding, the diet, delivery mode, and antibiotic use during the first 3 years of life were taken from their physical health records for both case and control group.

Results: 15.6% of overweight children received antibiotic within the first three months when compared to 3.5% of controls which is statistically significant (p&LT; 0.01). During the first year of life 84% of overweight children received at least one antibiotic compared to 53% of controls (p&LT; 0.01). Furthermore, 92% of them received antibiotics during the first three years of life and 82% of controls. In the group of overweight children it can be seen that they were more frequently (>6 times) prescribed an antibiotic therapy in the first three years of life than their healthy weight peers (i.e. 32.8% of overweight children vs 8.4% of controls). The antibiotics were mostly prescribed due to upper airway and ear infections and children mostly received narrow-spectrum penicillins, followed by broad-spectrum penicillins and macrolides. In addition, 55.2% of overweight children were breastfed less than three months or were entirely formula fed and 14.9% of them were born with caesarean section. In addition, higher body weight at 3 years of age was strongly associated with a higher body mass index at the age of 8, regardless of the gestation weight.

Conclusion: Antibiotic exposure and repeated use during the first 3 years of life was associated with overweight at 8 years of age. Such consequences of antibiotic use might be one of many reasons for childhood obesity epidemic. This also highlights the importance of careful use of antibiotics during early childhood.

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Status of elements important for bone metabolism in serum of children with inflammatory bowel disease and healthy controls in reference to their eating habits

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Introduction: Vitamin K, vitamin D and Calcium take part in bone metabolism. Among children requirements for those elements is the greatest due to rapid bone growth. Their insufficient intake with diet may have an impact on the peak bone mass appearance time as well as on osteoporosis risk in adulthood. Pediatric patients with inflammatory bowel disease (IBD) seem to be prone to vitamin K, vitamin D and calcium deficiency due to ongoing inflammation and poor intake.

Aim: To assess the circulating levels of calcium, vitamin D, undercarboxylated (inactive) osteocalcin (ucOC), carboxylated fraction of osteocalcin (cOC) and ucOC; cOC ratio (UCR) (indicator for vitamin K2 status), in healthy children and children with IBD in reference to their dietary intake.

Subjects and methods: In a pilot prospective study 24 children were enrolled (15 healthy and 9 with IBD in clinical remission), mean age was 12 years. From each participant a blood sample was obtained for cOC and ucOC levels analysis with ELISA kits and vitamin D3 and calcium concentration using standard methods. Additionally a quantitative evaluation of studied vitamins dietary intake was obtained using 24-hour interview and analyzed by ALIANT computer program. Nutritional habits were assessed using a questionnaire.

Results: In both studied groups poor implementation of recommended vegetables and fruit daily intake was observed (only 22% ate vegetables and 33% fruits every day). None of the children studied ate those products more than once a day. Thus approximately only 34% of norm for vitamin K and 32.6% for vitamin D (56%-for controls, 45%-IBD group) was realized. Calcium intake was also poor (46.7% for IBD group and 56%-for controls). Milk was consumed more frequently by children from control group (p=0.0196). The median ucOC serum concentration in whole examined group equaled 34.30 ng/ml [7.37-37.51; SD-8.37], it was 32.29 ng/ml [20.38-37.51; SD-5.48] in healthy children and 35.03 ng/ml [7.37-36.40; SD-12.03] in IBD group. The median UCR serum concentration was 1.85 [0.94-4.30; SD-1.04] in the healthy group and 1.11 ng/ml [0.48-3.46; SD-1.15] in IBD group. The median vitamin D serum concentration was surprisingly low in both groups, especially in healthy children- 15.40 ug/ml [10.00-44.80] compared to the IBD group - 27.20 ug/ml [20.40-43.30] (p=0.0027). Only 7/24 (29%) children received vitamin supplementation daily, 6 from the IBD group and only 1 from the healthy group.

Conclusion: Children do not implement recommended norms for vitamins K, vitamin D and calcium dietary intake. Our laboratory results suggest deficiency of vitamin K2 (high ucOC UCR levels) and vitamin D3 in both examined groups. We found that both vitamin K2 and vitamin D3 deficiencies were higher in the control group then the IBD group in clinical remission. Further studies on larger groups are required.

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**Objectives and Study:** Bone mineralization is influenced by environmental factors like hormones and nutrition already from fetal life. The bone development during childhood is important for peak bone mass and thereby for bone health in adult life. Sparse data are available for preschool children. The aim of the present study was to investigate relations between bone mass and body composition, nutrition, biomarkers and lifestyle in healthy 4-yr-old.

**Methods:** One-hundred eleven children (53 girls), 20% being overweight, were investigated. Anthropometry was measured with stadiometer and dual-energy X-ray absorptiometry (DXA) (Lunar DPX-IQ, GE Lunar Corp, Madison, WI, USA). Nutritional intake was estimated from 7 days recording. Plasma phospholipid fatty acids were determined with capillary GC. Physical activity was calculated from questionnaire. Statistical methods included multiple regression analyses and confounders.

**Results:** Bone mineral content (BMC) and total bone mineral density (BMD), and of femoral neck (BMD$_{FN}$) and lumbar spine area differed by gender in normal weight but not in overweight children. There were strong correlations between the bone parameters and the LS2-LS4 area to z-scores for weight, height and BMI and to lean body mass (LBM) (all p<0.001) but also to fat mass and BMAD (all p<0.001). Total energy and carbohydrate intake but not total fat intake correlated to all bone measures and protein and phosphate to all but spinal area. Vitamin D intake was not correlated to bone mass but children with the lowest quintile of vitamin D plasma concentration had lower BMD (p<0.01). Five children with milk intolerance and lower calcium intake had significantly higher calcitonin values, 12.9 vs 8.0 ng/L (p=0.025). Calcitonin correlated negatively to spine area and BMD in spine and femoral neck. Serum concentrations of calcium and phosphorus correlated with BMC, total BMD and spinal area. Leptin correlated with spinal BMD (p=0.02). Linoleic acid intake was positively correlated to bone markers in normal weight but not overweight children without difference in intake. No correlation was found to omega-3 fatty acid intake. In overweight children there were strong negative correlations between BMD and serum linoleic acid concentrations (r=-0.58, p=0.009), total n6 (r=-0.61, p=0.03) and ratio n6/n3 (r=-0.64(p<0.003), but positive to DHA and total n3 fatty acids (r=-0.57, p=0.02 and r=0.54, p=0.03, respectively). DHA and total omega-3 fatty acids were also positively correlated to BMC in normal weight children (r=0.27, p=0.02 each). Influence of daily activity was not significant but might be dependent on the fact that actinometers were not accepted by the children.

**Conclusion:** Bone mass had strong correlation to anthropometric measures and nutrition, including fatty acid composition, which seem to be of importance for bone mineralization and density in 4-yr-old children.

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Nutritional status and energy intake evaluation for children with gastrointestinal food allergy

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Objectives and Study: Evaluation of complaints, physical growth and development and energy intake for children suffering from the gastrointestinal food allergy.

Method: Ninety seven children with the confirmed diagnosis 'gastrointestinal food allergy' have been examined in the department of paediatric gastroenterology, hepatology and nutrition of Federal Research Centre of Nutrition and Biotechnology - 52 (53.60%) boys and 45 (46.93%) girls aged from 6 months to 16 years. The children were divided into 4 age groups: I group - 15 (15.46%) children aged from 6 to 11 months; II group - 56 (57.73%) children (1-4 years of age); III group - 16 (16.49%) children (5-10 years of age); IV group - 10 (10.31%) children (11-16 years of age). All the children passed the anthropometric investigation, total IgE level measurement and specific IgE-antibodies level measurement (to cow milk protein (CMP) and gluten). The anthropometric data were evaluated using the WHO Anthro (children up to 5 years of age) and WHO Anthro Plus (children older than 5 years of age) programs. The evaluation of home food intake and its energy value has been performed for 35 patients.

Results: The main complaint (disturbance of stool's quality and frequency) was detected in 78 (80.41%) children: stool of 50 (51.55%) children was too frequent and liquid; constipation was registered among 28 (28.86%) children. 75 (77.32%) children complained about the abdominal pain; the flatulence was observed in 71 (73.20%) children; 75 (77.32%) children complained about the low/selective appetite. Total IgE level’s median was 51 [14; 238] MU/ml. The increase of the specific IgE-antibodies to CMP was detected in 52 (53.61%) children; to gluten - in 30 (30.93%) children; the combined IgE sensitization (to CMP and gluten) was revealed in 27 (27.84%) children. The results of anthropometric evaluation showed that 44 (45.36%) children had a body weight deficiency, 8 (8.25%) children complained about the low weight; the physical development delay (z-score height/age value less than -2) was identified in 15 (15.46%) children (in the I age group mainly). The energy intake corresponded to the age consumption norms in 2 (5.71%) children; the insufficient energy intake (due to deficit of fat intake mainly) was detected in 24 (68.57%) children; the excessive energy intake due to protein component - in 9 (25.71%) children.

Conclusion: The study has found out that the children suffering from the gastrointestinal food allergy get the unbalanced food intake and form the body weight deficiency and physical development delay risk group. The physical development delay most often could be detected in children within 1 year of age, which fact witnesses the growing organism's largest sensibility to the nutrient deficiency in this age period.

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Preventive effects of a combination of dietary scGOS:lcFOS and n-3 PUFA in a murine cow’s milk allergy model

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Objectives and Study: Cow's milk allergy (CMA) affects 2% of children younger than 4 years and no effective prevention or treatment strategies are available. The dietary components short-chain galacto- and long-chain fructo-oligosaccharides (scGOS:lcFOS) and omega-3 poly-unsaturated fatty acids (n-3 PUFA) have immune regulatory capacities and have been demonstrated to reduce the allergic symptoms in a murine model of CMA, however, it is unknown if an additional effect occur when these dietary components are combined. The objective of this study was to evaluate the preventive effect of a combination of scGOS:lcFOS and n-3 PUFA on CMA development in a mouse model.

Method: 3-4 weeks old C3H/HeOuJ female mice received a control or a supplemented diet with 1% (9:1) scGOS:lcFOS, 6% n-3 PUFA or a combination of 1% scGOS:lcFOS and 6% n-3 PUFA (n=12-15) from day -14. For 5 weeks (day 0-28) the mice were weekly sensitized to 20 mg cow's milk whey protein in PBS with 10 ug cholera toxin (CT) or CT only (control). Clinical parameters were measured after intradermal and oral challenge. After the mice were killed (day 43) mesenteric lymph nodes (MLN), spleen and lamina propria (LP) were isolated to measure the levels of Th1 and Th2 subsets. Serum was collected to determine levels of mouse mast cell protease 1 (mMCP-1) and antigen specific immunoglobulins.

Results: The scGOS:lcFOS diet or n-3 PUFA diet reduced the acute allergic skin response significantly. The combination diet showed no significant reduction of the acute allergic skin response. All the tested diets caused no significant reduction in CMA-induced mMCP-1 and immunoglobulins IgE, IgG1 and IgG2a serum levels. Th1 and Th2 subsets in spleen, MLN and LP were neither affected by CMA nor by the dietary supplementations.

Conclusion: A dietary supplementation with scGOS:lcFOS or n-3 PUFA in a preventive setting reduce the acute allergic skin response in CMA mice. No additional effect was observed when these components were combined. CMA appeared to have no influence on Th1 and Th2 subsets in spleen and gut-associated lymphoid organs.

Disclosure of interest: Johan Garssen and Leon M. J. Knippels are employees of Nutricia Research

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Feeding cows’ milk or follow-on formula for young children in the second year of life: observational data from the Childhood Obesity Project (CHOP)

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Objectives and Study: High dairy protein intake in infancy leads to an increase obesity prevalence at school age (1). Observational studies have also associated total animal and dairy protein intakes in toddlers with increased BMI at later ages (2). Many follow-on formulae for young children (FOFYC) have a lower protein content than cows’ milk (CM). We explored whether the choice of milk fed in the second year of life was associated with BMI-z-score and overweight/obesity at 6 years of life in children participating in the European Childhood Obesity Project (CHOP) Trial that consumed different protein content infant formula (low protein: LP or high protein: HP) or were breastfed (BF) in the first year of life.

Methods: Out of 528 children who participated in the CHOP follow-up visit at 6 years of age, 278 were included according to the following eligibility criteria: having a food diary for at least 2 days at 12 and 24 months of age; having anthropometric data at 12, 24 and 72 months of age; not consuming cow’s milk as a drink but FOFYC at 12 and 24 months and during the second year of life (FOFYC); not consuming FOFYC but CM at 12 and 24 months and during the second year of life (CM group). Length/height, weight, BMI z-scores were calculated. Overweight and obesity at 6 years of age were defined according to World Health Organization criteria. Linear regression models were used to analyze the associations of BMI z score at 6 years and milk feeding in the second year of life. Fisher’s exact test was used to assess significant group differences in overweight prevalence.

Results: Out of 278 children, 236 consumed CM and 42 FOFYC. Feeding of choice (CM or FOFYC) did depend on the country (Belgium: 8 of 26 receiving CM; Germany: 0/27; Italy: 105/107; 30/44; Spain: 66/74; P< 0.001). The BMI-z score tended to be lower in children previously consuming FOFYC (β= -0.36, P= 0.053). This results did not change when feeding group during infancy (BF/LP/HP) was included (β= -0.35, P=0.06). Overweight and obesity tended to be lower in children previously consuming FOFYC (P= 0.25) (Table).

<table>
<thead>
<tr>
<th>Type of milk feeding and BMI status</th>
<th>Cows’ milk n=236</th>
<th>Follow-on formula for young children n=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td>60 (25.4)</td>
<td>7 (18.6)</td>
</tr>
</tbody>
</table>

Conclusion: Feeding follow-on formula for young children in the second year of life was associated with a non-significant trend to lower BMI z-score and less overweight/obesity at 6 years of life than feeding cows’ milk. Interpretation of the results is limited by a small sample size and potential confounding. Data from prospective randomized trials are needed to evaluate the impact of dairy protein supply in toddlers on later obesity risk.

Acknowledgement: Financially supported in part by the Commission of the European Communities, Project Early Nutrition (FP7-289346), and the European Research Council Advanced Grant META-GROWTH (ERC-2012-AdG 322605).
References:

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Oral therapy among children fed by gastrostomy or nasogastric tube

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Objectives and Study: Home Enteral Nutrition (HEN) program is applied to patients with at least 50% of daily nutritional requirement provided with feeding via gastrostomy or nasogastric tube. It leads to reduction of oral feeding as well as frequency of swallowing stimulation. Children required enteral nutrition due to lack of sufficient skills in oral feeding and swallowing should be included in systematic logopedic and/or feeding/swallowing therapy. Such a therapy gives a chance to increase oral feeding rate, or even enable complete discontinuation of enteral nutrition. The aim of the study was to verify whether this group receive logopedic and feeding/swallowing therapy more frequently than the patients participating in HEN due to other reasons.

Method: Patients enrolled to the HEN because of inadequate skills in oral feeding (n=65) were compared with patients qualified to HEN due to increased nutritional needs and malnutrition resulting from other causes(n=47). Data regarding logopedic and feeding/swallowing therapy were collected during routine check-ups, related to participation in HEN. The appropriate chi square tests were used to compare data distribution between both groups.

Results: 36 out of 65 (55%) patients had logopedic and 17 out of 65 (26%) swallowing therapy provided in the group with inadequate skills in oral feeding, whereas in the group of patients receiving HEN due to other reasons these were 21 out of 51 (41%) and 10 out of 51 (20%) respectively. The data distribution between groups did not vary significantly.

Conclusion: Presented outcomes suggest that, patients qualified to HEN programme on account of insufficient oral feeding and swallowing skills, that need and require professional therapy in the field of feeding and swallowing, do not receive suitable assistance in this matter.
The effect of early nutrition intervention on insulin sensitivity and pancreas PANDER expression in IUGR rats

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Objectives and Study: Epidemiological studies have linked intrauterine growth retardation (IUGR) to insulin resistance during adult life. Pancreatic-derived factor (PANDER) is a uniquely structured protein strongly expressed within and secreted from the endocrine pancreas and plays a role in pancreatic islet apoptosis. This study was to investigate the effect of early nutrition intervention on insulin sensitivity and pancreas PANDER expression in IUGR rats.

Methods: Forty-eight neonatal male IUGR rats were established by maternal food restriction throughout the period of pregnancy. They were randomly divided into IUGR control group (n=24) and isocaloric high-protein nutrition intervention IUGR group (n=24). Twenty-four normal neonatal male rats were used as normal control group. The rats in IUGR control group and normal control group were breastfed for 3 weeks and their mothers were provided free access to basic diet. They were provided free access to basic diet until 12 weeks of age after weaning. The rats in nutrition intervention IUGR group were breastfed for 3 weeks and their mothers were provided free access to high-protein diet. They were provided free access to high-protein diet until 4 weeks of age after weaning. They were provided free access to basic diet from 4 weeks to 12 weeks of age. The basic diet was prepared according to the ingredients of America Institute of Nutrition Purified Rodent Diet 93 for growth. The available protein was 20% of total calorie of basic diet. The high protein diet was lower in cornstarch (100g/kg) and higher in available casein (100g/kg) compared with basic diet. The available protein was 30% of total calorie of high protein diet. At 4 and 12 weeks of age, fasting blood glucose and insulin were measured and homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated. Western blot assay was used to detect the expression of pancreas PANDER.

Results: At 4 weeks of age, there were no significant differences in HOMA-IR (IUGR control group: 1.26±0.32; nutrition intervention IUGR group: 1.24±0.26; normal control group: 1.23±0.20. n=12, P>0.05) and pancreas PANDER expression (IUGR control group: 1.04±0.30; nutrition intervention IUGR group: 0.97±0.24; normal control group: 1.00±0.20. n=6, P>0.05) among each group. At 12 weeks of age, HOMA-IR was significantly higher in rats of IUGR control group (2.34±0.46) than rats of nutrition intervention IUGR group (1.72±0.38) and normal control group (1.76±0.36) (n=12, P<0.01). There were no significant differences in HOMA-IR between the rats of nutrition intervention IUGR group and normal control group (n=12, P>0.05). At 12 weeks of age, pancreas PANDER expression was significantly higher in rats of IUGR control group (1.42±0.27) than rats of nutrition intervention IUGR group (0.98±0.26) and normal control group (1.00±0.24) (n=6, P<0.05). There were no significant differences in pancreas PANDER expression between the rats of nutrition intervention IUGR group and normal control group (n=6, P>0.05).

Conclusion: PANDER may play a role in the impaired insulin sensitivity and pancreatic development of IUGR rats. Early nutrition intervention with isocaloric high-protein diet may promote the recovery of the fetal impaired pancreatic cells, avoiding insulin resistance during adult life of IUGR.

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The prevalence of stunting among children under five in Indonesia by socio-economic status

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Objectives and Study: This analysis aimed to obtain insights on prevalence of stunting among various age groups of children under-five years of age by economic status in Indonesia.

Method: A sub-analysis on the prevalence of stunting by age group and by socio-economic was conducted using the National Health Survey data (Riskesdas) 2013. The prevalence was re-analyzed in accordance to following age groups: 0-5, 6-11, 12-23, 24-35, 36-47, and 48-59 months old and by economic status (Quartile 1 to 5 of Household welfare index, Quartile 1 is the lowest economic status and Quartile 5 is the highest). The index was constructed based on scoring of the following criteria: main source of drinking water, cooking fuel, latrine facilities, type of closet, final stool disposal site, source of lighting, ownership of motorcycle, TV, water heater, gas tube of 12 kg, refrigerator and car.

Results: Among children 0-12 months who are severely stunted, the highest prevalence was found in the Q4 or middle high- socio-economic group (23.5% for 0-6 months, 23.0% for 6-12 months), while the lowest was in the Q1 lowest socio-economic group (15.6% for 0-6 months, 17.9% for 6-12 months). Similar for stunting, the highest prevalence was found in middle high-economic group for 0-6 months (23.5%), and in middle-economic group (26.7%) for 6-11 months. (Figure 1). For children of 12-23, 24-35, 36-47 and 48-59 months old, the prevalence of stunting was consistently the highest in Q3- and Q4 socio economics and the lowest in Q5- socio-economics. Further information on the etiology of stunting and the prevalence of infection in various socio-economic group need to be further explored.

Conclusion: Contrary to common belief, prevalence of stunting among children from various age groups was the highest in middle high- and middle socio-economic as compared to those from the lowest group.

Keywords: stunting, high socio economic status, children under five

Disclosure of interest: All authors are full-time employee of Danone Nutricia Early Life Nutrition-Indonesia

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